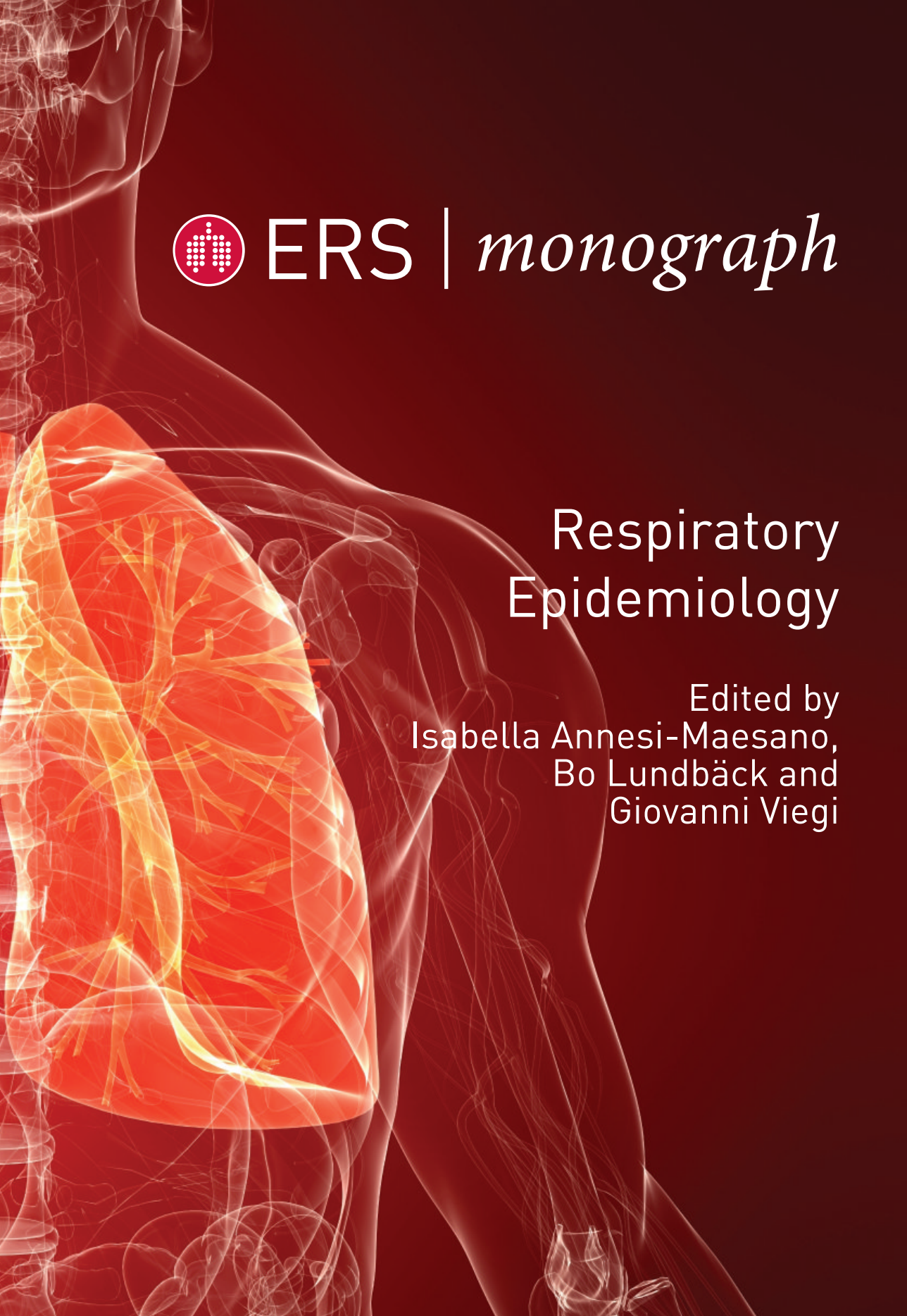

ERS | *monograph*

Respiratory Epidemiology

Edited by
Isabella Annesi-Maesano,
Bo Lundbäck and
Giovanni Viegi

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Editor in Chief
Tobias Welte

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Tobias Welte, Editor in Chief

Pulmonary diseases affect millions of patients every year worldwide. COPD, asthma and allergies are among the most widespread, affecting more than 5% of the total population. Diseases induced by cigarette smoke, such as chronic bronchitis, COPD and lung cancer, can be avoided, but intense social and political engagement is required in order for disease prevention programmes to succeed.

Research into the pathophysiology and genetics of pulmonary diseases has increased greatly in the last decade. This has led to new developments in lung cancer treatment and new therapies for asthma; in addition, COPD and interstitial lung fibrosis have been evaluated and are now included in treatment guidelines. The level of development in this area of respiratory medicine is highlighted by the establishment of the first causal therapy for cystic fibrosis with genetic modifiers, and the improvement in long-term prognosis in pulmonary hypertension patients using a combination of various drugs.

In the past, treatment of respiratory conditions took place outside the major cities, mainly because TB was one of the major diseases. Pneumology was therefore only marginal a part of internal medicine. Fortunately, this has gradually changed over the years, in some countries more than others. Today, pneumology is almost at the centre of internal medicine. This opens new fields of interest where respiratory medicine overlaps with many other disciplines. Some of the most important areas of overlap are: oncology in the field of thoracic neoplasms; cardiology for pulmonary hypertension; infectious diseases connected with pneumonia and TB; intensive care for patients with respiratory failure and the severely ill; dermatologists and ear, nose and throat specialists in allergology; neurologists and psychiatrists in sleep medicine; and geriatricians and palliative care physicians involved in the care of patients with terminal illnesses.

This issue of the *ERS Monograph* demonstrates the development of respiratory medicine convincingly. It provides an overview of

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the essential epidemiological figures for all who work in respiratory diseases. It should also be used to increase the visibility of respiratory medicine, and could serve as a basis in political negotiations about the need for increasing budgets for respiratory medicine.

I want to congratulate the Guest Editors Isabella Annesi-Maesano, Bo Lundbäck and Giovanni Viegi for their tremendous work in setting up this important *Monograph*. I am convinced that readers will find it useful in their daily work.

Guest Editors

Isabella Annesi-Maesano

Isabella Annesi-Maesano is the NIH Research Director and Professor of Environmental Epidemiology at the Universities Pierre and Marie Curie (UPMC) and René Descartes (both Paris, France), and Director of the Dept of Epidemiology of Allergic and Respiratory Diseases (EPAR) (www.epar.fr) at the Institute Pierre Louis of Epidemiology and Public Health of the French NIH and the UPMC in Paris. In 2013, she was appointed as a member of the Directoire at the Observatory for the Sciences of the Universe "Ecce Terra" at UPMC. She is an active member of several professional societies, including the European Respiratory Society (ERS), the American Thoracic Society (ATS), the European Academy of Allergology and Clinical Immunology (EAACI) and the International Society for Environmental Epidemiology (ISEE). She is currently a member of the ERS Environmental and Health Committee, and Chair of the EAACI Interest Group Aerobiology and Air Pollution. She previously served as a member of the ERS Executive Committee, Chair and Secretary of the Occupation and Epidemiology Assembly, and Chair and Programme Secretary of the Respiratory Diseases section of the International Union Against Tuberculosis and Lung Disease. She serves on several editorial boards, including the *European Respiratory Journal*, the *European Respiratory Review* and *Allergy*.

Isabella Annesi-Maesano was trained as a respiratory epidemiologist after a double curriculum in physics and medicine, and a PhD in epidemiology and biostatistics. Her personal research interest focuses on the distribution and aetiology of asthma, COPD, interstitial pulmonary diseases and rhinitis using an exposomic approach (the internal and external environmental stressors an individual encounters in their lifespan, particularly their early life), and identifying phenotypes/endotypes. Her research has been funded by the French Ministries of Health, Research, and Environment and Sustainable Development, the French Environmental Agency (ANSES), the European Commission, and others. Since 2013, she has coordinated the interdisciplinary translational research project HEALS (Health and Environment-wide Associations based on Large population Surveys) part of the

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FP7-ENV (7th Framework Programme for EU Research: Environment) programme, integrating clinics, epidemiology, toxicology, omics, sociology and other disciplines to advance understanding about respiratory diseases through exposomics. The study is recruiting new birth cohorts of singletons and monozygotic and dizygotic twins in Europe that will be followed over a course of time. She has more than 300 papers and chapters in peer-reviewed journals and books. She collaborates with 30 international institutions.

Giovanni Viegi

Giovanni Viegi is acting Director of the CNR Institute of Biomedicine and Molecular Immunology (Palermo, Italy), leader of the Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology (Pisa, Italy), and Contract Professor at the Faculty of Environmental Sciences of the University of Pisa. He graduated in Medicine *magna cum laude* and specialised in pulmonology and occupational medicine.

Giovanni Viegi is a member of the Executive Committee of the Italian Society of Respiratory Medicine (SIMeR), Past President of the European Respiratory Society (ERS), the Italian representative for the Global Alliance against Chronic Respiratory Diseases (GARD), and is a member of the American Thoracic Society (ATS) and the International Union Against Tuberculosis and Lung Disease (IUATLD). From 1998 to 2001 he was a member of "Technical-scientific Committee for elaboration of law proposals in the matter of indoor pollution" at the Italian Ministry of Health.

Giovanni Viegi's main research interests and areas of grant coordination are: lung function assessment; the epidemiology of COPD in relation to air pollution; respiratory occupational medicine; respiratory allergology; the epidemiology of cardio-respiratory and psychiatric comorbidity; and clinically controlled smoking cessation.

With the Pisa research group, he has conducted the two largest respiratory epidemiological longitudinal studies on general population samples in Italy (in the Po Delta and Pisa areas).

Giovanni Viegi serves on the editorial boards of the *Medicina Respiratoria*, the official journal of the Asociación Argentina de Medicina Respiratoria, and the *Rassegna di Patologia dell'Apparato Respiratorio*, the official Journal of the Associazione Italiana Pneumologi Ospedalieri (AIPO). He is the author of 299 original articles (198 in English), 56 book chapters (19 in English) and 140 proceedings (49 in English).

Bo Lundbäck

Bo Lundbäck is Professor of Respiratory Epidemiology at the Institute of Medicine/Krefting Research Centre at the University of Gothenburg (Gothenburg, Sweden). He is affiliated with the Dept of Respiratory Medicine and Allergy at the Institute of Public Health and Clinical Medicine University of Umeå (Umeå, Sweden), and the Dept of Research and Development at the County Council of Norrbotten (Luleå, Sweden).

Bo Lundbäck is currently the Head of the Occupation and Epidemiology Assembly of the European Respiratory Society (ERS) and a member of the Society's Executive Committee, Science Council, Environment and Health Committee, and Tobacco Control Committee. He is Associate Editor of *Respiratory Medicine* and a member of the editorial board of the *Journal of Chronic Obstructive Pulmonary Disease* and the *European Clinical Respiratory Journal*. He was one of the editors of the *The European Lung White Book*, second edition.

Bo Lundbäck's research mainly focuses on clinical respiratory epidemiology and he has been the scientific leader of several large-scale epidemiological and clinical studies, as well as health economics studies. The main studies in which he has been involved include: the Obstructive Lung Disease in Northern Sweden (OLIN) Studies, which have been in progress since 1985 with more than 50 000 participants; and the FinEsS Studies, which compare the epidemiology of asthma, allergy, COPD and respiratory symptoms in Finland, Estonia and Sweden. He is co-chair of the West Sweden Asthma Study, which covers epidemiology, clinical research, and research on cellular mechanisms, including proteomics and genetics.

He has supervised more than 20 PhD students from several countries, including Sweden, Finland, the USA, Estonia and Vietnam, and has collaborated closely with several universities and hospitals in Europe and worldwide, from the University of Virginia (Charlottesville, VA, USA) in the west to Hanoi Medical University (Hanoi, Vietnam) in the east. He has more than 170 publications on PubMed.

ERS | monograph

Introduction

Isabella Annesi-Maesano[1,2], Bo Lundbäck[3] and Giovanni Viegi[4,5]

Fifteen years ago, officers of the Occupation and Epidemiology Assembly of the European Respiratory Society (ERS) had the idea of disseminating the concepts and results of the respiratory epidemiological studies carried out in Europe to the membership of the ERS. Thus, in the year 2000 the Respiratory Epidemiology in Europe issue of the *ERS Monograph*, edited by Isabella Annesi-Maesano, Amund Gulsvik and Giovanni Viegi, was published [1]. It covered a broad spectrum of topics, including COPD, study design, and environmental and behavioural risk factors. In all, there were 21 chapters: seven were methodological, five were devoted to specific diseases, and nine dealt with risk factors. The book helped generate an understanding of the importance of epidemiology as a basic component of medical culture, and was an important advocacy tool. Indeed, a few years later, the ERS and the European Lung Foundation (ELF) published the first edition of the *European Lung White Book* [2], which was instrumental to the ERS' success in convincing the European Commission (EC) of the need for including respiratory and allergic diseases amongst the diseases for which funding was planned in FP7 (7th Framework Programme for EU Research) [3]. Last year, the ERS published the new version of *The European Lung White Book* [4], an updated advocacy tool that will generate more attention and research funding for respiratory medicine.

Respiratory epidemiology has greatly advanced in last 15 years. It has allowed us to fill gaps in the knowledge about major respiratory diseases and to investigate them further. It is now time to launch the updated edition of the Respiratory Epidemiology *ERS Monograph*.

This update of the *Monograph* considers the advances that have been accomplished by respiratory epidemiology in contributing to a better understanding of respiratory health and disease prevention. The updated version covers a broader spectrum of topics than the first version and includes 21 chapters: seven are devoted to the most commonly encountered respiratory diseases, 10 consider risk factors, two focus on methodology, and two discuss the economic burden of major respiratory diseases. In a changing world, the updated *Monograph* addresses new or poorly treated issues at the population level, such as poverty, air pollution (a growing burden due to climate change), rhinitis, interstitial lung diseases and obstructive sleep apnoea (which are increasing in prevalence), and also covers epigenetic–environment interactions when appropriate.

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Most of the authors are members of the Occupation and Epidemiology Assembly of the ERS. The Assembly is active in developing epidemiology and several leading persons from large-scale local and international studies, as well as research consortiums, such as ECRHS (European Community Respiratory Health Survey), ISAAC (International Study of Asthma and Allergies in Childhood), GA^{2}LEN (Global Allergy and Asthma European Network), BOLD (Burden of Obstructive Lung Disease) and GOLD (Global Initiative for Chronic Obstructive Lung Disease), are members of the Assembly. The work of the Assembly increases knowledge about environmental, occupational and lifestyle factors, such as the risks of developing respiratory diseases, and also considers factors that contribute to respiratory health [5]. The Epidemiology Group and the Occupational and Environmental Health Group are deeply involved in these studies. Special interest is paid, among others, to the most important single risk factor for respiratory disease, smoking, and the work of the Tobacco, Smoking Control and Health Education Group focuses on the severe and hazardous effects of active and passive smoking. As a result of the increase in understanding about the importance of the interaction of genes and the environment, a fourth Group, Genes and Environment, recently started activities.

One of the most important tasks of the Occupation and Epidemiology Assembly is advocacy. During the presidency of Giovanni Viegi two important advocacy committees were established: the Tobacco Control Committee (TCC) and the Environment and Health Committee (EHC). The TCC was preceded by the Smoking Prevention Committee, established in 1998. The committees work closely with the ERS Brussels office, the ERS Headquarters and the ELF in lobbying for respiratory health in Europe, and worldwide *via* the World Health Organization (WHO). The Assembly collaborated with WHO in the foundation and management of the Global Alliance against Chronic Respiratory Diseases (GARD). Both committees organise evening sessions at the European Parliament and informative activities for the EC. Another example of the committees' activities was the EHC initiative to organise the first international conference held by a respiratory society on the health effects of climate change [6].

The Assembly has organised several conferences and task forces, and has produced *Monographs* and important position papers, among them position papers on the respiratory effects of air pollution and occupation [7, 8]. Recent task force reports include updated recommendations on epidemiological studies of COPD [9] and occupational asthma [10]. Members of the Assembly were also part of the Editorial Boards of both the first and the second editions of the *European Lung White Book* [2, 4].

Perspectives

It is important that healthcare providers and society as a whole know about the prevalence and trends of prevalence and incidence of major disease, including the respiratory diseases. Large-scale population studies are necessary for the calculation of prevalence of, for example, COPD and asthma. Information from registry data is not enough to calculate the prevalence of COPD in society, as under-diagnosis is huge; large-scale epidemiological studies that include spirometry are required. The diagnosis of asthma is arbitrary, and irrespective of international guidelines, asthma has in reality been classified differently in many parts of the world, including Europe. Thus, population studies also provide important information about asthma, and international studies allow comparison of prevalence between areas and countries.

Prevalence studies, *i.e.* cross-sectional studies, may provide data about risk factors for diseases; however, a found association could be a cause, a consequence of disease or a parallel phenomenon. Thus, longitudinal studies of cohorts of the general population are needed as these studies provide more valid results regarding risks, and the probability of the associations being risks is greater than that of the associations that are derived from cross-sectional studies. These important methodological aspects have been explored in a chapter of this *Monograph*.

One important area that requires consideration is rare respiratory disease. In Europe, a disease or disorder is defined as rare when it affects less than one in 2000 people; however, as many as 30 million people may be affected by one of over 6000 rare diseases. It has been shown that many major diseases can be subdivided into individual diseases called phenotypes, some of which are classified as rare. This is often the case with respiratory disease. Rare diseases constitute appropriate models for the underlying mechanisms of other diseases. The specific features associated with rare diseases (low individual patient numbers, diversity, geographical location) mean that research needs to be developed at a large level in order to optimise funding, infrastructures and technological platforms. Patient registries and databases are key to the development of epidemiological and/or clinical research in this area, as they pool data and achieve a sufficient sample size, leading to improvements in patient care and healthcare planning. The creation of a rare respiratory disease registry would also be a powerful tool in creating a network of experts.

Due to the increasing difficulty and cost of carrying out new general population surveys, in which a progressively decreasing proportion of people agree to participate, it is likely that there will be rise in the epidemiological use of routinely collected statistics, as well as medical records stored by family practitioners. Data mining procedures within the huge database created by the widespread use of e-health instruments (patient diaries, electronic health cards, *etc.*) will help.

Another important issue that needs to be developed in the future is exposomics. Genetics have been found to account for only around 10% of diseases, and the remaining causes appear to be environmental. In order to understand the causes of respiratory disease and its prevention, the impact of the environment needs to be further investigated. Exposomics can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to his/her health. In respiratory disease, an individual's exposure begins before birth with passive smoking and includes insults from the environment, like air pollution, diet, lifestyle and occupational sources, and their interactions with characteristics such as genetics, epigenetics and physiology. This requires appropriate methodologies, such as epidemiology, biostatistics, omics and data mining.

Respiratory epidemiology also plays an important role in translational research, and molecular epidemiology is increasingly important. Modern translational research covers epidemiology, clinical aspects (including phenotyping or endotyping) and research on cellular mechanism (including inflammation, proteomics and genetics). The contribution of epidemiology can guarantee a representative sample for study. Studies of the gene–environment interaction play an increasing role in modern epidemiological research.

We believe that in this issue of the *Monograph* the reader will find methodological information and content that will be useful in forthcoming calls for research proposals issued by the EC within the framework of Horizon 2020, which includes relevant themes for public health and respiratory medicine.

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List of abbreviations

AIDS	Acquired immune deficiency syndrome
ALRI	Acute lower respiratory infection
ARDS	Acute respiratory distress syndrome
BCG	Bacilli Calmette–Guerin
BHR	Bronchial hyperresponsiveness
BMI	Body mass index
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DALY	Disability-adjusted life years
DLCO	Diffusing capacity of the lung for carbon monoxide
FeNO	Exhaled nitric oxide fraction
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
ICU	Intensive care unit
Ig	Immunoglobulin
IL	Interleukin
IQR	Interquartile range
LRTI	Lower respiratory tract infection
NSCLC	Nonsmall cell lung cancer
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
PEF	Peak expiratory flow
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SDB	Sleep-disordered breathing
TB	Tuberculosis
TNF	Tumour necrosis factor

Chronic obstructive pulmonary disease

Bo Lundbäck[1], Per Bakke[2,3], Truls Ingebrigtsen[4], Peter Lange[5,6], Anne Lindberg[7], Joan B. Soriano[8] and Jørgen Vestbo[9,10]

COPD is today the third leading cause of death worldwide and its prevalence has steadily increased. Prevalence in Europe seems to be levelling, and in western and northern Europe, recent data even indicate a decrease. Beyond tobacco, other major risk factors have been identified, while objective possibilities for prevention exist. New medicines and treatment strategies can slow down disease progression. COPD heterogeneity is huge and restricts treatment options, and epidemiology can contribute to identifying clinically relevant phenotypes of COPD.

The first generally agreed classification of obstructive airway diseases was made at a symposium organised mainly by British researchers in 1959, the CIBA Guest Symposium, and definitions of asthma, chronic bronchitis and emphysema were decided upon [1]. With few exceptions, the definitions were adopted within a few years by, for instance, the World Health Organization (WHO) and the American Thoracic Society (ATS). The term COPD is young, first being used in the early 1960s [2]. Initially, it covered emphysema and the obstructive form of chronic bronchitis, and asthma with chronic obstruction has been handled differently over the years. The term COPD was used in parallel with the obstructive form of chronic bronchitis and emphysema for several decades, and still in the 1970s and 1980s, most researchers used the latter term, such as FLETCHER *et al.* [3] in their well-known book *The Natural History of Chronic Bronchitis and Emphysema*. The diagnosis of COPD requires chronic airway obstruction and symptoms typical of the disease or known exposures associated with COPD [4, 5]. COPD was regarded as a single disease entity, and still is in the care of patients and in managing the disease. However, today COPD is regarded as a broad syndrome and not a single disease entity [4, 5].

Since the 1990s, efforts have been made worldwide to define COPD more homogenously, but as recently as 1995–1997, the guidelines defined the disease differently [6–8]. COPD was defined as an irreversible airway obstruction. Another view was presented by the Global

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Initiative for Chronic Obstructive Lung Disease (GOLD) consortium, and COPD was defined as a not fully reversible airway obstruction and, furthermore, that symptoms should be treated [9]. Since 2000, the British National Institute for Health and Care Clinical Excellence [10] has adopted several of the disease criteria suggested by the GOLD, as did the ATS/European Respiratory Society (ERS) statement regarding disease severity, with few exceptions (table 1) [4].

During the last decade, attempts have been made to find clinically relevant measures beyond lung function in the assessment of the severity of COPD. Among them, the BODE index was suggested, a composite measure based on BMI, airflow obstruction, dyspnoea and exercise capacity [12]. Recently, the GOLD consortium launched new guidelines suitable for treatment of COPD, and a classification also aiming to evaluate the level of symptoms and the risk of future exacerbations [5]. This assessment of patients includes symptoms, severity of airflow limitation and a history of exacerbations in a way that categorises the patients into four categories: A, B, C and D. Also comorbidities should be assessed. This new GOLD classification for guiding of treatment is already under evaluation and results are slightly conflicting [13, 14].

The development of the understanding of the disease is reflected by several excellent reviews on the epidemiology of COPD [15–21]. The focus of this chapter is to give an update on the prevalence, mortality and morbidity of COPD, review recent data on incidence, discuss the still huge underdiagnosis of COPD, summarise major risk factors and comorbidity, and finally review recent results on biomarkers of disease progression.

Results of studies of the prevalence and incidence of COPD are largely influenced by how COPD has been defined, the representativeness of the reference equations used for lung function, the age composition of the studied samples and their smoking habits, and the burden of other exposures [22–24].

To study the prevalence and incidence of COPD, population surveys using post-bronchodilator spirometry of representative samples of the general population are needed. It is not possible to use registry data to measure the true prevalence of COPD due to large underdiagnosis as well as some misclassification. Despite the general agreement on the need

Table 1. Classification of the severity of COPD according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) and Global Initative for Chronic Obstructive Lung Disease (GOLD) criteria

ATS/ERS	
Mild	FEV_1/VC <5th percentile of predicted and FEV_1 ⩾70% pred
Moderate	FEV_1/VC <5th percentile of predicted and FEV_1 60–69% pred
Moderately severe	FEV_1/VC <5th percentile of predicted and FEV_1 50–59% pred
Severe	FEV_1/VC <5th percentile of predicted and FEV_1 35–49% pred
Very severe	FEV_1/VC <5th percentile of predicted and FEV_1 <35% pred
GOLD	
Mild	FEV_1/FVC <0.70 and FEV_1 >80% pred
Moderate	FEV_1/FVC <0.70 and FEV_1 ⩾50% to <80% pred
Severe	FEV_1/FVC <0.70 and FEV_1 ⩾30% to <50% pred
Very severe	FEV_1/FVC <0.70 and FEV_1 <30% pred, or FEV_1/FVC <0.70, FEV_1 <50% pred and chronic respiratory failure

VC: vital capacity. Reproduced and modified from [11] with permission from the publisher.

for spirometry for diagnosing the disease, debate still exists over how the disease should be defined. A strict physiological definition of obstruction is the use of the 5% lower limit of normal (LLN), which has been suggested by several researchers [4], while in clinical practice and research, the fixed FEV_1/FVC ratio of <0.7 suggested by GOLD is mostly used [5, 9]. Both definitions have disadvantages. The fixed ratio overestimates COPD among the elderly and tends to underdiagnose COPD in young adults. The LLN fails to diagnose COPD in the elderly, even in very severe COPD cases with severe emphysema and low FEV_1 and FVC. A recent ERS Task Force gave priority to the LLN but acknowledged the use of the fixed ratio [25].

Prevalence of COPD

Population surveys have identified large differences in the distribution of the prevalence of COPD [26]. As COPD is not very common among young adults, most studies have targeted middle aged and elderly subjects. Studies of the prevalence of COPD include the international, large-scale Burden of Obstructive Lung Disease (BOLD) study [27] and its predecessors, such as PLATINO [28], and PREPOCOL in Colombia even earlier, and several local studies have followed the BOLD protocol. In addition, the European Community Respiratory Health Survey (ECRHS) and its follow-up studies have contributed data on the prevalence of COPD among young and middle-aged adults, and more recently on incidence [29]. Furthermore, there are several country-based and local or regional studies that have provided important contributions to the knowledge about both the prevalence and the incidence of COPD. Some single-centre, large-scale population studies including COPD have been in progress for decades: in Oslo, Norway since 1972; in Copenhagen, Denmark since 1976; in the Po River region in Italy since 1980; and since 1985 in Bergen, Norway and northern Sweden [30–34]. These studies have contributed data on the prevalence, and some on the incidence, of COPD.

The BOLD study has presented data in subjects aged >40 years using both the fixed ratio (GOLD) criteria and the $LLN_{5\%}$, and the prevalence varied from 10% to more than 25% using the fixed ratio criteria, and about 60% of the prevalence based on the fixed ratio when using the $LLN_{5\%}$ [24]. GOLD severity stage $\geqslant 2$ has been regarded as "clinically relevant COPD" [35] and these BOLD study results are presented in figure 1.

Countries where the prevalence of smoking has been decreasing for decades, such as most of the Scandinavian countries, have a relatively low prevalence of COPD GOLD stage $\geqslant 2$ of slightly more than 5% [36–39]. The previous large sex difference has now decreased considerably, particularly in northern European countries. Some studies indicate a decrease in the prevalence of COPD. The Spanish EPI-SPAN, 10 years after the IBERPOC, shows a clear decrease in the prevalence of COPD and a dramatic decrease in prevalence of GOLD stage $\geqslant 2$ (fig. 2) [40].

Incidence of COPD

There are still few studies on the incidence of COPD. These studies have defined COPD using the fixed ratio criterion, while reports of asthma among those with chronic airway obstruction have been handled differently. The first reports that allowed calculation of the incidence of COPD using modern criteria of the disease came from Scandinavian countries [41–45] and from the ECRHS [29].

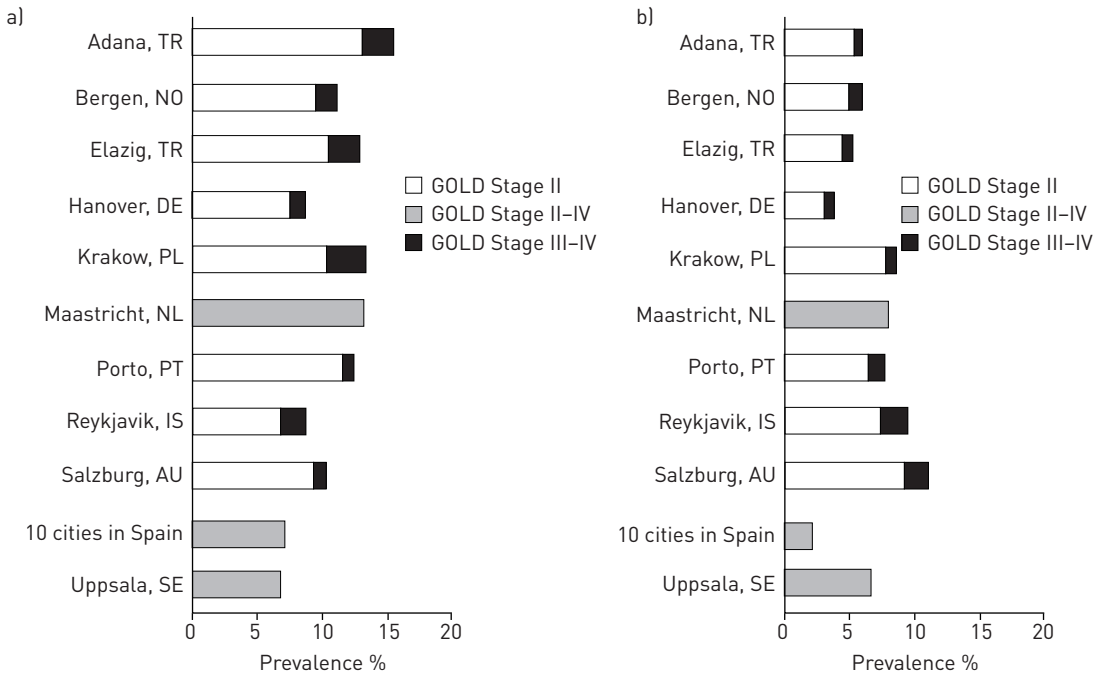

Figure 1. Prevalence of COPD in a) males and b) females aged ⩾40 years in European cities, by Global Initiative for Obstructive Lung Disease (GOLD) stage, ranked by national prevalence of current smoking. Data from multiple publications resulting from the Burden of Obstructive Lung Disease study. Reproduced and modified from [11] with permission from the publisher.

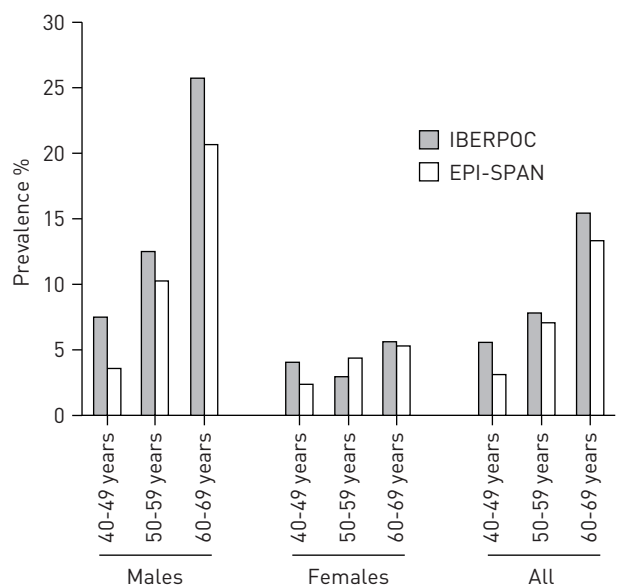

Figure 2. Changes by age and sex in prevalence of COPD in Spain from 1997 to 2007. Reproduced and modified from [40] with permission from the publisher.

As for prevalence, these Scandinavian studies found the incidence of COPD to be quite uniform in three countries, as well as the associated risk factors, mainly smoking, increasing age, and a predisposed condition with chronic cough and sputum production. In the Norwegian Bergen–Hordaland studies, the incidence over 9 years was one case per 100 persons per year with no sex difference among those aged 18–74 years at study start, and 10 times higher in smokers than in nonsmokers [42]. In the Swedish OLIN (Obstructive Lung Disease in Northern Sweden) studies, the annual incidence rate among smokers was estimated at 11 cases per 1000 per year *versus* two cases per 1000 per year among nonsmokers [44]; furthermore, about one out of four incident cases with COPD had an average annual decline of FEV_1 of >90 mL [43]. A 25-year follow-up survey from the Copenhagen City Heart Study of subjects aged 30–60 years at entry found that 39% of male and 30% of female smokers had developed COPD (GOLD), while the corresponding figures among nonsmokers were 5% and 9%, respectively [45]. The incidence of COPD has also been estimated in the ECRHS II among subjects aged 20–44 years at entry and was 2.8 per 1000 per year [29].

Mortality and morbidity

According to WHO World and Europe Mortality database, the age-standardised mortality rate varied considerably in Europe, with the highest rates in Denmark, the UK, Ireland, Iceland, Belgium and Hungary with >25 per 100 000; the lowest in France, Switzerland, Croatia, Latvia and Estonia with <10 per 100 000; and the average being about 20 per 100 000. According to death certificates, on average, COPD accounts for 3% of all causes of death in Europe. Overall, more males than females die from COPD; however, this sex difference does not occur in many countries in northern Europe, such as Denmark and Sweden [46]. As a result of the huge underdiagnosis, COPD is probably underreported in the death certificates, and data from several eastern European countries are even more scarce [11].

In addition, hospital admission rates vary considerably in Europe and the average is about 200 per 100 000, *i.e.* 10 times greater than the mortality rates [46]. Days spent in hospital due to COPD are decreasing, particularly in northern and western Europe, due to several reasons including probably more active treatment but also structural changes in the healthcare systems [11]. Mortality within 1 year of a COPD hospitalisation was 23% in the Netherlands [47], and the 3-month mortality was 15% and in-hospital mortality was 7% in the UK [48].

Underdiagnosis

As clearly indicated by the European Lung Foundation, recorded prevalence, hospital admissions and deaths are only the "tip of the iceberg" [49]. Considering the 505 million people in the 28 European Union countries, among the 260 million who are 40 years and older, it has been estimated that 23 million have COPD of moderate or higher severity and 17 million have stage I COPD [50]. With a minimum COPD underdiagnosis rate of 70%, it can be extrapolated that 28 million Europeans are not yet diagnosed, therefore remaining untreated.

Underdiagnosis of COPD remains constantly high in Europe and elsewhere, with figures ranging from 70% to 90% and even higher (fig. 3) [51]. These estimates of COPD underdiagnosis are substantially higher than those reported for high blood pressure, hypercholesterolaemia and other similar conditions.

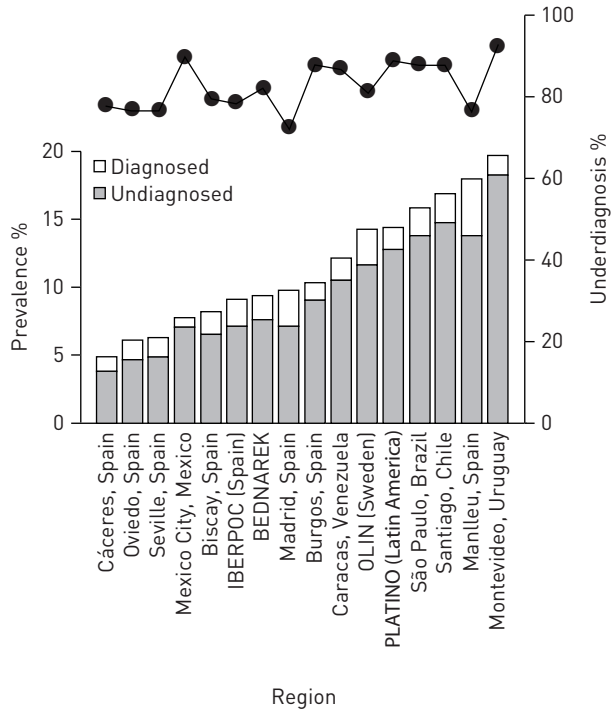

Figure 3. Reported prevalence of COPD and related underdiagnosis in selected population studies. Reproduced and modified from [51] with permission from the publisher.

At the individual level, undiagnosed airflow obstruction has a dose–response relationship with several unspecific adverse health effects like poor general health status, difficulty when walking or carrying weight, and even needing help with personal care [52]. In the very elderly, there are limitations in quantifying COPD burden [53]. Recent advances in reference equations, now valid in those aged up to 95 years, may facilitate quantification and reduce the magnitude of its related burden [54]. Regrettably, previous attempts to determine the specific reasons for COPD underdiagnosis at the population level and to relate it to smoking patterns, ageing, poverty, sedentarism, COPD mortality rates, or other related indicators at the international or national level, have been unsuccessful [38, 55–59].

Accurate diagnosis of COPD is important in order to initiate timely risk factor modification and therapy, and to avoid unnecessary costs and potential side-effects in those unlikely to benefit from therapy. The former implies basically offering smoking cessation according to locally available resources, while the latter requires other hygiene interventions, vaccinations, avoidance of sedentary living and individualisation of management within the current wealth of treatment options.

To reduce underdiagnosis, most important is the routine use of spirometry in primary care in all patients with respiratory symptoms. Furthermore, two main strategies can be envisaged, mass screening with spirometry and case-finding strategies. Both have advantages and limitations but in both, collaboration with primary care physicians and nurses is fundamental [51, 60]. There are a number of initiatives exploring the use of unconventional settings like pharmacies, and exploring the single or combined use of questionnaires, such as the COPD Population Screener [61], with other tools like peak flow with a threshold of 2.2 $L \cdot s^{-1} \cdot m^{-2}$

prebronchodilator [62], COPD-6 [63] or combinations of them, again with a balance of strengths and limitations [64].

Regrettably, the rate of false positives is not often reported in population surveys with spirometry but without conclusive evidence either way, the risks associated with misdiagnosis are minimal and there is no evidence that elderly individuals with newly identified airflow obstruction or mild COPD are overtreated with respiratory drugs, but are merely advised to reduce risk factors like smoking. Yet the individual and population burden associated with COPD underdiagnosis will remain high for the foreseeable future.

Risk factors

There are several risk factors for COPD. The current knowledge of risk factors for COPD is mostly based on cross-sectional community surveys; however, data have also been derived from longitudinal studies. When assessing the results, one should also bear in mind that different definitions of COPD have been used. The importance of different risk factors may vary throughout life, and depend on the coexistence of other risk factors and even the given phenotype of COPD in question. When assessing risks, quantifications of exposure play an increasing role [65]. As smoking rates decline, the relative importance of other risk factors is likely to increase. In addition, other factors like the airway microbiome may turn out to be of importance for COPD development. "Omics" analysis may be key to an improved understanding of the mechanisms of the various risk factors.

One of the ERS main pillars is advocacy, and an important focus of advocacy is smoking and air pollution with the aim of better respiratory health and health in general [66, 67]. The following, summarised in table 2, is a brief overview of the most important risk factors for COPD.

Smoking

Cigarette smoking is by far the most important causal risk factor for COPD in the Western World [21, 36, 37]. Although smoking rates have been on the decline in Europe and North America for some decades, the prevalence of current smoking is still above 20% in most European countries [68], and smoking rates are still increasing in Africa, South America and Asia [69, 70]. The risk of COPD increases with younger age of smoking uptake, daily smoking consumption and total cigarette exposure in terms of pack-years [21]. There are indications that females are more susceptible to smoking than males [71]. This might be due to smaller lungs in females than males, with higher exposure per unit of lung volume in females than males given the same level of exposure. In addition, sexual differences in the

Table 2. Risk factors for COPD

Cigarette smoking
Indoor air pollution
Early life events
Occupational airborne exposure
Socioeconomic status
Outdoor air pollution
Genetic susceptibility

metabolism of nicotine and inflammatory response to smoking might be of importance [72]. The percentage of smokers developing COPD reaches 50% [36, 37].

Indoor air pollution

An estimated 3 billion people are exposed to smoke from biomass fuel compared with about 1 billion people who smoke tobacco, which suggests that exposure to biomass smoke might be the biggest risk factor for COPD globally [73]. The most common sources include wood, charcoal, other vegetable matter, animal dung and coal. About 50% of deaths from COPD in developing countries are attributable to biomass smoke, of which about 75% are females [74]. A majority of homes in China, India and sub-Saharan Africa use biomass fuel for cooking, and in rural areas of Latin America, the proportion is also high [73]. In developing countries, females are traditionally responsible for cooking, so the exposure is highest for them and their young children, especially as infants are often carried on the mother's back. Typically, exposure to high concentrations of air pollutants lasts for 3–7 h per day [74]. Passive smoking *in utero*, in early life and in adulthood is independently related to an increased risk of COPD in adult life [75, 76].

Occupational airborne exposure

Occupational exposures to both inorganic and organic dust as well a variety of gases are risk factors for COPD, independent of smoking [77]. Examples are exposure to cotton textiles [78], jute processing [79], farming [80], wood workers [81], welding [82], foundry work [83], coal mining [84] and non-mining industrial dust [85]. 15–31% of prevalent cases of COPD have been attributed to occupational exposures [86, 87]. Work-related respiratory diseases including COPD have recently been reviewed in an ERS position paper [88].

Outdoor air pollution

The role of ambient air pollution in the development of COPD remains uncertain [89]. Several studies assessing the effect of mostly traffic-related air pollution on morbidity and mortality of COPD indicate a causal relationship. There are also plausible biological mechanisms and good evidence that air pollution affects lung development in childhood and triggers exacerbations in COPD patients. However, a recent review of the risk of ambient air pollution in COPD concluded that larger studies with longer follow-up periods, specific definitions of COPD phenotypes, and more refined and source-specific exposure assessments are needed to clarify this question [89].

Early-life events

The development of the bronchial tree is completed in terms of numbers of terminal bronchioles by the first trimester of pregnancy. The final number of alveoli is established by the age of 2 years [90] Thereafter, growth and functional development of the bronchial tree and the alveoli continue until about the mid-20s and last to the mid-30s, after which they decline [90]. Exposures to airborne agents and other events such as airway infections during this developmental phase of life are related to increased COPD. A longitudinal analysis from the ECRHS showed that subjects with early-life disadvantage including maternal asthma, paternal asthma, childhood asthma, maternal smoking and childhood respiratory infections have permanently lower lung function, no catch-up with age and a slightly larger decline in

lung function, and therefore a substantially increased COPD risk [91]. In addition, low birth weight is an independent risk factor for COPD that is associated with poor lung growth [92].

Socioeconomic status

Poor socioeconomic status is a risk factor independently associated with COPD and low lung function [93]. It is likely to be indicative of other factors such as intrauterine growth retardation; poor nutrition with a low intake of antioxidants; poor housing conditions; childhood respiratory-tract infections; exposure to tobacco smoke, biomass smoke and other indoor air pollutants; and occupational risks. These factors might collectively contribute to the risk of COPD. The magnitude of the effect on lung function of socioeconomic status, although variable, has been estimated over a lifetime at about 300 mL FEV_1 in males and more than 200 mL FEV_1 in females [94].

Genetic susceptibility

The fact that many smokers do not develop COPD and the family aggregation of the disease indicate a genetic susceptibility to COPD [37]. The most important known genetic risk factor for COPD is α_1-antitrypsin deficiency. Candidate-gene and genome-wide studies have found several other susceptible loci in genes related to COPD. These loci are mostly single-nucleotide polymorphisms [95, 96]. However, they contribute only a small proportion of the heritability of COPD and many findings have been inconsistent. Improved and previously unused genetic techniques, including copy number variation and epigenetic studies, and gene–gene and gene–environment interaction analyses, may alter this picture [97].

Comorbidity

Patients with COPD suffer often from other chronic diseases [98, 99]. A number of papers describe the prevalence and characteristics of comorbidities and their importance for the diagnosis, prognosis and treatment of COPD. This interest in extrapulmonary features of COPD is in line with the general recognition that patients with chronic diseases often have substantial multimorbidity and that the treatment of patients will be most effective if these multimorbidities are taken into account [100].

Both in epidemiological studies of the general population (in general practice, among patients followed in COPD clinics) and in patients enrolled in COPD trials of new drugs, the prevalence of comorbid conditions in addition to COPD is very high [100–103]. The most prevalent comorbidities are: cardiovascular diseases; diseases of the locomotor system including osteoporosis; mental health disorders, in particular anxiety and depression; gastro-intestinal disorders; cancer; and endocrine disorders. Although the comorbidities are most prevalent in the older patients, younger individuals living in deprived areas also have COPD together with depression, and cardiovascular and painful disorders as comorbidities [100].

Possible mechanism behind multimorbidity in COPD

The two most likely explanations for the high level of multimorbidity in patients with COPD are common risk factors and the presence of systemic inflammation [104]. The average patients with COPD in developed countries are around 70 years of age and have often a high cumulative tobacco exposure. In addition, there is an overrepresentation of COPD among

individuals with short school education and occupational exposures to dusts and fumes [104]. Both advanced age and smoking are important risk factors for most of the comorbidities seen in COPD and can, together with low level of physical activity, explain several comorbidities [105].

As COPD and many other chronic diseases are associated with low-grade systemic inflammation, it has been suggested that chronic inflammation could be responsible for the accumulation of comorbidities in COPD [98, 104]. Indeed, studies show that COPD individuals with persistent systemic inflammation have highest risk of comorbidities and exacerbations [102, 106–108]. Yet other studies suggest that the importance of systemic inflammation in COPD may be most relevant in continuous smokers and that systemic inflammation is not an obligate characteristic of obstructive lung function impairment as such, as comorbidities including cardiovascular disease were low in a large sample of never-smokers with airflow limitation [109]. In addition, it seems that meticulous adjustment for cardiovascular risk factors can explain most of the cases of ischaemic heart disease seen in COPD [110, 111].

Consequences of comorbidities

There are several consequences of comorbidities in COPD. Some of the consequences are related to the diagnosis as comorbidities, in particular heart disease, may blur the diagnosis of COPD and comorbidities may be underdiagnosed as they share similar symptoms with COPD [112–114]. In addition, comorbidities have an important impact on health status, prognosis, and the treatment that can be offered to a patient, and impair the effect of pulmonary rehabilitation [115, 116]. The presence of severe COPD may also make treatment of some comorbidities demanding surgical procedures impossible.

In a prospective study of the general population, comorbidities significantly worsened the prognosis of COPD in a dose-dependent manner and contributed to 5-year mortality beyond the adjustment for the severity of COPD based on FEV_1 [101]. Recently, the BODE collaborative group suggested a comorbidity index for COPD, the COTE index, in memory of the late respiratory researcher Claudia Cote [102]. This index includes comorbidities like cancer, anxiety, liver cirrhosis, atrial fibrillation, diabetes, pulmonary fibrosis, congestive heart failure, coronary heart disease, and gastric and duodenal ulcers. Similarly to the well-known Charlson index, scale value points are assigned to each of the comorbidities, which are then summed [117]. In the initial study investigating the predictive value of this new index, the COTE score significantly improved survival prediction compared with the predictive ability of the BODE index [102].

The clinical importance of different comorbidities varies with the type of comorbidity. Pragmatically, comorbidities could be divided into those that should not be overlooked, because they are treatable, and those that are not that important, because they are not possible to treat. The former includes osteoporosis, depression and heart disease. However, even those less prone to treatment, such as cognitive impairment, are important when choosing the right inhalation device or offering pulmonary rehabilitation.

Biomarkers

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [118]. Biomarkers important in clinical medicine include

diagnostic, prognostic or physiological status information. We usually limit the use of the term biomarkers to markers in blood and exhaled air, and in clinical research, induced sputum and, potentially, bronchoalveolar lavage fluid.

The use of biomarkers in COPD epidemiology is often limited by costs and the time required to obtain material for a biobank can pose limitations. In addition, some biomarkers may be associated with the cause of COPD, *e.g.* tobacco smoking, rather than the disease itself. In addition, there is some evidence that at least biomarkers reflecting systemic inflammation may differ between smoking-induced COPD and COPD in never-smokers [109].

Biomarkers of disease, disease severity and vital prognosis

A large number of biomarkers have been examined to date [119, 120]. Several biomarkers can differentiate COPD from smokers and nonsmokers [119, 120] but the value of this may be questionable. Several previously suggested biomarkers relate to the risk of hospital admission but as this is almost entirely driven by exacerbation risk [121–124], it may not be related to severity of the disease *per se*. Biomarkers such as C-reactive protein (CRP) and fibrinogen also relate to vital prognosis in population-based studies as well as patient cohorts [121, 122, 125, 126]. In a recent large patient sample, a whole array of biomarkers increased the predictive value of mortality [127]; however, most of these markers have not yet been examined in the general population.

Biomarkers of disease activity

Most biomarkers that associate with disease characteristics such as FEV1 are likely to reflect disease severity rather than disease activity [128]. Only a few biomarkers that associate with progression of disease have been examined. Using FEV1 decline as the measure of progression, STANESCU *et al.* [129] found an association between neutrophils in sputum and FEV1 decline but the association was, in fact, inverse, *i.e.* FEV1 decline was associated with subsequent neutrophil count. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, club cell protein was associated with FEV1 decline whereas markers of systemic inflammation were not [130]. The club cell protein findings were supported by biomarker analyses of the Lung Health Study [131]. In the Hokkaido COPD Study, eosinophils were associated with FEV1 decline [132]. These findings have not been examined in population-based settings. In epidemiology, a biomarker of subclinical COPD reflecting ongoing damage in airways or lung parenchyma would be of significant value. Studies have suggested surfactant protein D as a potential marker [133, 134], although studies in more established disease are less convincing [130, 135].

Computed tomography (CT) scans are increasingly used in clinical COPD studies and to some extent in epidemiology [136]. CT-defined emphysema is a strong predictor of both incident airflow limitation [137] and FEV1 decline [130, 132]. It may be possible in future COPD epidemiology to examine predictors of lung tissue loss using serial CT, as in patient samples [138] and in lung cancer screening [137, 139].

Biomarkers associated with exacerbations

Exacerbations are important outcomes in COPD and responsible for a major burden in many patients. In clinical research, there is clearly a need for biomarkers of exacerbations, similar to troponin in myocardial infarction. Serum amyloid A has been proposed [140] but

presumably with little use in epidemiology, where prediction of exacerbations has been studied in more detail. Markers of systemic inflammation, such as CRP, fibrinogen and white cell count, all seem to have some value [121–125]. In patient samples, they may have little value as individual markers, when adjusting for history of exacerbations [32]. However, when used in combination they perform better [108] and recently, a large, population-based Danish study found a significant predictive value also after adjusting for history of exacerbations [107]. Interestingly, the COPD Biomarker Qualification Consortium, comprising academic researchers as well as industrial partners [141], are in the process of obtaining recognition of fibrinogen as a biomarker for stratifying patients in trials examining risk of exacerbations.

Biomarkers of comorbidities

Comorbidities are frequent in COPD and often affect both the clinical manifestations of COPD and prognosis. CRP has been shown to predict cardiovascular morbidity [142] an, in a population-based study, a combination of three biomarkers was predictive of an array of comorbidities [106].

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Chapter 2

Asthma and rhinitis

Deborah Jarvis

Asthma and rhinitis are common chronic diseases in children and adults. Both conditions show marked geographical variation in disease prevalence, and the prevalence of each has increased over the past 60 years in many, but not all, parts of the world. Children who have regular contact with other children early in life either within their family or by attending day care have less rhinitis, and this "protection" appears to last into adult life. However, these exposures do not appear to be as beneficial for asthma. There has been intense and extensive research into associations of lifestyle (smoking, diet and obesity) and environmental factors (infections, allergen exposure, farming environments and pollution) with both asthma and rhinitis, but the underlying causes for the geographical variation and temporal trends remain unclear.

Asthma and rhinitis are common chronic conditions in children and adults. Many people with asthma also have rhinitis (and *vice versa*). As both diseases show strong associations with sensitisation to common allergens, their co-existence is often attributed to a shared link with IgE, even though the two diseases can occur together in children and adults who have no evidence of atopy. There has been a marked increase in the prevalence of asthma and rhinitis over the past decades and some risk factors are common to both conditions.

Prevalence of disease and geographical variation

Asthma

The prevalence of asthma within a population is highly dependent on the definition used, and in epidemiological studies asthma has been defined by: 1) symptoms suggestive of disease; 2) diagnosed disease; and 3) physiological measures including measurements of airway responsiveness. Two large international studies, the European Community Respiratory Health Survey (ECRHS) [1] and the International Study of Asthma and Allergy in Children (ISAAC) [2], developed standardised questionnaires for the assessment of asthma and asthma-like symptoms during the early 1990s, which continue to be used by many researchers today.

The ISAAC and ECRHS studies showed large variations in the prevalence of asthma between countries [3, 4], a higher prevalence of asthma in English speaking countries and, in the

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ISAAC study in particular, a lower prevalence in many parts of the developing world. In ISAAC, the national 12-month period of prevalence of wheeze in 6–7-year-olds ranged from ~2% to 36%, and in ECRHS from 4% to 32% (the prevalence of current asthma in ECRHS ranged from 2% to 12%).

The geographical patterns were mirrored in the World Health Survey [5, 6], and are broadly supported by variations in airway responsiveness (AHR) to methacholine in adults [7]. In children there was only a weak correlation between study centre prevalence of AHR to saline and centre prevalence of wheeze, even though AHR to saline was associated with wheeze at an individual level [8]. Such inconsistencies may be explained by the strong relationship of AHR with atopy (country-specific prevalence of wheeze was related to country-specific prevalence of AHR within the atopic population) and, perhaps, by infections, which cause transient increases in AHR.

Use of health services is dependent on health-seeking behaviour, access, the way in which healthcare services are organised, and on the underlying information technology to capture events. Therefore, the value of health service utilisation data to estimate disease prevalence remains limited, despite some evidence that variations in hospital admission rates may reflect variation in disease prevalence in both children and adults [9, 10].

Asthma mortality is rare, and much more common in the elderly. Furthermore rates depend on local death certification practice, the underlying prevalence of disease and case-fatality rates. Although of limited value for assessing disease prevalence, asthma mortality rates may hold some value for asthma surveillance within countries with similar healthcare provision [11]. The Global Burden of Disease study collated mortality data from across the world for 1990 and 2010, and showed that globally life expectancy had increased, and all cause age-standardised mortality had decreased [12]. Age-standardised mortality rates for asthma also decreased over this period, such that asthma ranked only 42nd as the most important cause of years of life lost by 2010. However, reflecting its high prevalence, asthma was an important cause of years living with a disability (ranked 14th globally) [13] and DALY (ranked 28th globally) [14].

Rhinitis

Allergic rhinitis, defined as "a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose", produces symptoms of rhinorrhoea, nasal obstruction, nasal itching and sneezing [15]. However, surveys often directly ask whether participants have "hay fever" or "nasal allergies" or whether nasal symptoms are present with eye symptoms "when you did not have a cold or the flu". These are often accompanied by questions on seasonality (to separate seasonal from perennial rhinitis), although the recent ARIA (Allergic Rhinitis and Its Impact on Asthma) guidelines [15] suggest that information on whether symptoms are persistent (that is if symptoms last for >4 days·week^{-1} for >4 consecutive weeks) or intermittent are preferred.

Both the ECRHS and ISAAC have shown substantial variations in the prevalence of "hay fever and nasal allergies" [3] and "allergic rhinoconjunctivitis" [4, 16]. In general, higher levels of hay fever are observed in communities with higher levels of asthma, although there are exceptions to this. In most communities, the prevalence of rhinitis is higher than the prevalence of asthma (~2–39% in 6–7-year-olds and 9–40% in adults). As rhinitis is rarely

fatal and many people with rhinitis can obtain effective nonprescription medications over the counter, mortality and health service utilisation data provide little insight into disease prevalence.

Time trends

Asthma

Over the past 60 years many studies have reported increases in asthma prevalence in children and young adults [17]. This has been supported indirectly by increases in hospital admissions [18–20] and general practice consultations [21] for asthma. These changes have sometimes [22, 23], but not always, been accompanied by increases in airway responsiveness [24]. The discrepancy can possibly be explained by the more widespread use of inhaled corticosteroids [25], increased reporting of mild disease and lower thresholds for diagnosing disease. During the 1990s, hospital admissions for asthma in several developed nations decreased but sales of drugs for the treatment of asthma showed marked increases [26].

Of note the increases in asthma prevalence have occurred at the same time as increases in the prevalence of sensitisation to common inhalant allergens in both children and adults [27–31], whether tested by skin prick tests or by serum specific IgE.

More recently, some studies suggest the steady increase in asthma prevalence is now slowing or even reversing. The repeat ISAAC survey [32, 33] showed that over the previous decade the prevalence of asthma in 6–7-year-olds and in 13–14-year-olds had increased in some parts of the world and decreased in others, although the geographical patterns of change in older children did not mirror the pattern of change in the younger children [32]. In Sweden, repeat adult surveys in three different parts of the country suggest that while the prevalence of diagnosed asthma has increased over the past 20 years, the prevalence of symptoms commonly associated with asthma has remained stable or even fallen [34–36]. This is very similar to the pattern of change seen in adult cohorts followed over the same period [37]. However, at the same time countries such as Italy have shown a steady increase in symptoms of asthma [38].

Rhinitis

Many epidemiological studies reporting increases in asthma prevalence also report increases in hay fever [22, 39]. The ISAAC study has described these changes in many centres across the world, in both 6–7-year-olds and 13–14-year-old children [32].

Phenotypes of asthma and rhinitis

Clinicians have long recognised different phenotypes of asthma using terms that relate to the assumed underlying biological process (*e.g.* allergic asthma), the timing of disease onset (*e.g.* adult-onset asthma) and triggers to symptoms (*e.g.* premenstrual asthma). More recently there have been calls for greater recognition and better definition of the different patterns of disease (phenotypes) within epidemiological studies [40].

From the wealth of longitudinal epidemiological data available in children, phenotypes of wheeze have been identified using latent class analysis. These approaches have identified phenotypes such as "transient", "intermediate-onset", "late-onset" and "persistent" [41, 42]

wheeze and are highly compatible with observations made in the Tucson cohort study several years earlier using less sophisticated statistical methods [43]. Similar efforts among adults taking part in two large epidemiological studies showed four phenotypes, largely defined by allergic status, age of onset of disease and disease activity: 1) active treated allergic childhood-onset asthma; 2) active treated adult-onset asthma; 3) inactive/mild untreated allergic childhood onset asthma; and 4) inactive/mild untreated nonallergic adult-onset asthma; all of which showed some stability over time [44, 45]. Further efforts incorporating more biological markers of disease in those with adult-onset severe asthma reported three more potential groups: 1) severe eosinophilic inflammation predominant; 2) low sputum eosinophils, frequent symptoms, high healthcare use; and 3) mild-to-moderate well controlled [46]. These classifications may be of use in identifying different risk factors for each phenotype [47].

In comparison with asthma there has been relatively little published work on rhinitis phenotypes even though clinicians recognise various forms of disease (for example occupational rhinitis and vasomotor rhinitis). Chronic rhinosinusitis, another common nasal disorder [48] that shares some symptoms of rhinitis, and indeed may be a long-term consequence of allergic rhinitis, has been associated with asthma [49], and may be associated more strongly with some specific phenotypes of asthma [50].

Natural history and prognosis

Asthma

Many adults with asthma will have experienced symptoms for the first time in childhood. As with many chronic diseases, age-specific incidence rates are not as commonly reported as prevalence estimates. Furthermore, because asthma has a relapse and remitting clinical course it may be difficult for study participants to accurately recall the age when symptoms began for the very first time. More than 40 years ago, in a prospective study, YUNGINGER *et al.* [51] showed that incidence rates for asthma were far higher in young children than older children and adults (~10 per 1000 per year in children aged between 1 and 4 years, and about one per 1000 per year in young adults). A similar pattern was seen in the British 1958 birth cohort [52]. In the Nurses' Health Study the incidence of adult-onset asthma in middle-aged females was ~1.5 per 1000 per year [53], and a recent report from Canada suggested the incidence of physician-diagnosed asthma in adolescents was between 8 and 10 per 1000 per year [54]. Differences in rates may be due to different incident asthma definitions and differences in the populations studied.

Asthma is more common in children than adults and is, in part, related to birth cohort related increases in disease prevalence, and to the remission of disease in some children, often during adolescence [52, 55]. Boys have more wheeze and asthma than girls, but by puberty these sex differences are less marked due to a higher incidence of asthma in adolescent girls compared to adolescent boys [52]. One detailed longitudinal study has shown that airway responsiveness becomes less severe during adolescence in boys, with little change or increasing severity in post-pubertal girls, particularly those with hay fever [56].

Children with the transient early wheeze phenotype may outgrow their symptoms later in life [43]. Those with more severe disease in childhood are the ones most likely to continue having symptoms in middle age [57]. In a large British cohort, only 15% of children who reported wheeze by the age of 5 years continued to report wheeze by the age of 16 years [58]. In another study, only 25% of those who had a history of asthma or wheezy bronchitis by the

age of 7 years reported wheeze in the past year at the age of 33 years [59]. In a study from Sweden, 80% of 7-year-olds with diagnosed asthma had evidence of disease by the age of 19 years [60]. Persistence of disease is more common in girls, those with AHR, and those who are atopic [61]. Remission over the adolescent period may not be permanent. Recurrence after prolonged remission has been reported to be more common in smokers and those with other allergic disease [59], in those sensitised to house dust mite, those with an earlier age of onset of symptoms in childhood, and those with airway responsiveness [62].

Lung function is a major determinant of health and independent living in adult life, and low lung function in adults with asthma is associated with increased overall mortality [62]. It has been proposed that asthma may influence adult lung function through several mechanisms, including failure of normal lung growth in children with submaximal attained lung function in early adult life, more rapid decline in lung function during adult life, and the development of fixed airways obstruction, secondary to inflammation. In a Norwegian cohort of 404 full-term children of mothers with asthma followed to the age of 7 years, 14% developed asthma. Children who developed asthma had worse lung function as neonates, and these differences were more marked by the age of 7 years strongly suggesting that while some of the lung function deficits occurred prenatally, post-natal lung development was adversely affected by asthma [63]. Post-bronchodilator spirometry in 35-year-old asymptomatic adults was lower in those who had wheezed before, but not after, the age of 7 years when compared to adults who had never wheezed. The lowest lung function was seen in adults who had wheeze and asthma throughout their life [64]. Although asthma may be associated with poor lung function there is some evidence that treatment with inhaled steroids may reduce these effects in children [65, 66]. Similarly, in adults the reported excess decline in lung function in those with asthma [67, 68] may be reduced by regular use of inhaled steroids [69], particularly in those with high total IgE [70].

Older adults with a history of asthma are at a greater risk of fixed airway obstruction [71]. One cross-sectional study that examined post-bronchodilator spirometry suggests the effect of asthma on airway obstruction may be equivalent to smoking 20 cigarettes per day [72].

There is limited evidence that people with asthma experience higher mortality rates than those without asthma, which is mainly being explained by excess deaths from respiratory disease [73].

Allergic rhinitis

Several studies suggest that hay fever is uncommon in preschool children, and peak incidence occurs in late adolescence and early adult life [55, 74, 75]. In a follow-up of over 24 000 UK children, primary care consultation records showed that by the age of 18 years about one in five children had been diagnosed with asthma, and about 12% were diagnosed with rhinitis. Within these groups, almost 80% of those with asthma by the age of 18 years had been diagnosed by the age of 7 years, compared to only half of those with hay fever [76]. As with asthma, rhinitis may remit, with about one-third of children with physician-diagnosed allergic rhinitis being asymptomatic by the age of 18 years [77]. A similar proportion of children with hay fever before the age of 16 years were asymptomatic by the age of 23 years [78].

Incident asthma is more common in those with a history of rhinitis, with risks being increased in those with hay fever of the longest duration and greatest severity, and in those with both sinusitis and rhinitis [79]. An increased risk of asthma in those with rhinitis is unlikely to be explained only by atopy as measured by skin prick tests and serum specific IgE [80]. Chronic sinusitis has

also been associated with the onset of cough and wheeze in children [81], and cross-sectional surveys suggest chronic rhinosinusitis is associated with adult-onset asthma [49].

Changes in atopy may influence asthma and rhinitis. It is likely that most of those who become sensitised to common allergens develop these responses in childhood. Incident sensitisation in adult life is relatively uncommon (although it does occur). It is hypothesised that in later life, ageing and immunosenescence may lead to remission of atopy in older people, but the extent to which lower prevalence of atopy in older adults (compared to younger adults) is explained by remission or cohort-related increases in atopy in younger generations requires further investigation. There are few cohort studies that have collected objective well standardised markers of atopy over an extended period into later adult life [82–84]. Furthermore, cautious interpretation of small changes in atopy as assessed by skin prick tests, and even by serum measures of specific IgE, is warranted because these tests are liable to measurement errors, and differential biases related to changes in reagents over time. The prevalence of positive serum specific IgE in adults up to the age of 55 years changed little over a 10-year period, with the size of the measured change being small in comparison to the probable size of the "laboratory error" [84].

Race

Racial differences in the prevalence of asthma and rhinitis in populations living in the same geographical regions have been reported. One of the largest studies included over 170 000 people living in San Francisco (CA, USA) who were members of the same health insurance programme. It suggested there was little difference in the prevalence of diagnosed and treated asthma between racial groups, but a much higher prevalence of hay fever amongst Asians compared to black and white subjects [85]. Other studies have examined racial differences in disease prevalence in the USA [86–88], Africa [89], New Zealand [90], Australia [91, 92] and the UK [93–95]. In the UK, Black African, Indian and Bangladeshi school children had a lower prevalence of asthma than white UK children [94], but mixed white/Black Caribbean had a higher prevalence. Whether such differences can be explained by genetic predisposition, exposure to environmental risk factors, socioeconomic status or cultural attitude to disease is unclear.

In some regions a substantial proportion of ethnic minority populations are first generation migrants, and the age at which migration occurs may influence disease prevalence amongst people who are from the same ethnic group and country of origin. In the UK, the prevalence of asthma is lower in young south Asian females than young white females, but within the south Asian population the prevalence of asthma is lower amongst those who migrated after the age of 5 years, compared to those who were born in the UK [95]. Similar patterns exist in children living in the UK from the Black Caribbean and the Black African population [94].

Socioeconomic status

The ISAAC study showed the prevalence of wheeze was lower in nations with lower national income, a pattern most clearly seen for recent wheeze in 13–14-years-olds, but not seen for wheeze or asthma in younger children, or for rhinitis [96]. In the World Health Survey there was a U-shaped pattern with higher prevalence of wheeze and asthma reported in low- and high-income countries, although the prevalence of diagnosed asthma increased with increasing wealth if only urban regions were considered [97].

At the individual level, low socioeconomic status may be associated with risk factors for development of disease, exposures that exacerbate disease and poor access to and utilisation of health services that lead to poor control of disease [98]. Associations of disease with socioeconomic status may have changed over time [99], but for hay fever, at least, disease is more strongly associated with parental social class than achieved social class in adult life [78], reflecting the importance of early life on the development of atopy and rhinitis.

Risk factors

Ecological analyses, in which country specific prevalence of disease is correlated with country specific prevalence of potential risk factors, is a common epidemiological approach. Although such associations may not reflect those seen at an individual level (the so-called "ecological fallacy"), when associations are seen, they may prompt further investigation. Using ecological analyses the ISAAC study [100] has shown that countries with a higher prevalence of wheeze in 13–14-year-olds were wealthier (higher gross national product) and had lower smoking rates amongst males, lower background particulate pollution levels, higher sales of paracetamol, and diets that were lower in calories from cereals and rice, lower in total protein from cereals and nuts, lower in starch and higher in trans fatty acids. These ecological associations were weak, but were broadly supported by similar associations for country-specific prevalence of wheeze in 6–7-year-olds and for rhinitis.

Family structure

In 1989 STRACHAN [101] reported a strong negative association of birth order with the prevalence of hay fever at ages 11 years and 23 years. This was not observed for asthma. It was proposed that exposure to older siblings in early childhood resulted in more infections, in turn leading to immunomodulation and a decreased likelihood of allergic disease. The negative association of rhinitis with birth order or family size has been replicated multiple times in different settings across the world [102], and differences persist into adult life. It is unlikely these differences are secondary to immunological changes in females with each pregnancy [103, 104], as the prevalence of rhinitis decreases with increasing number of younger siblings [101, 105, 106]. Furthermore children with no siblings who attend child care facilities early in life have fewer allergic symptoms [107, 108] than those who start attending day care later in life, again suggesting the "hygiene hypothesis" operates through post-natal mechanisms.

Exposure to many children in early life may protect against rhinitis, but the association with asthma is more complex with inconsistent results from studies [102]. There are reports of positive associations of birth order for asthma in low-income children [109] and globally [110], as well as positive associations of exposure to other children early in life and wheeze in adults [108]. These findings probably reflect the different effects of early infections on atopy, rhinitis and asthma.

Infections and parasites

Researchers have tried to identify specific infections that might explain the negative associations of allergic disease with exposure to other children. MATRICARDI and co-workers [111, 112] suggested that hepatitis A, *Toxoplasma gondii* and *Helicobacter pylori* may protect against asthma and hay fever in Italy and the USA. Within the National Health and Nutrition

Examination Survey, colonisation with *H. pylori* showed a strong negative association with asthma and rhinitis in children [113]. Although a history of measles infection was associated with lower levels of IgE sensitisation in Guinea Bissau, Africa, this probably arose from survivor bias with fewer atopic children being likely to have survived a severe measles epidemic [114]. More recent work in Brazil has shown no evidence that infection with hepatitis A, herpes simplex, herpes zoster, *H. pylori*, Epstein Barr virus or *T. gondii* influences the prevalence of wheeze in young children [115]. It is likely that some of these infections are markers of low socioeconomic status, and their associations are confounded by other exposures.

Vaccinations are a major public health strategy to reduce infections and in many parts of the world vaccination rates are high. In such communities, those who are unvaccinated are a small, highly selected proportion of individuals and observational studies examining their effect on asthma are difficult to interpret. One randomised controlled trial examining pertussis [116] and cohort studies examining a wider range of usual childhood vaccinations show little evidence of important associations [117, 118]. Although early BCG vaccination was initially reported to be protective for the development of allergic disease [119, 120] this has not been supported by more recent studies [121–123].

Viral upper respiratory tract infections cause exacerbations of asthma in children [124, 125] and adults [126]. Prospective studies show that rhinovirus-induced wheeze in early life predicts the presence of asthma later in childhood [127–129], an association that may be stronger in those with particular variants at the 17q21 locus (which has been strongly associated with asthma in children) [130]. There is considerable evidence that children who develop clinical disease related to infection with RSV are at a substantially increased risk of asthma [131,] but the link may not be causal [132].

A systematic review of the association of asthma with parasites concluded that *Ascaris* infection was associated with an increased risk, and hookworm infestation with a decreased risk [133]. Although *Schistosoma* may alter the allergic response [134], to date, it does not appear to reduce the risk asthma or hay fever [135]. Opportunities to examine the effect of parasites on asthma come from widespread community eradication programmes, but although such programmes may increase the prevalence of atopy (as measured by skin prick tests), there does not appear to be substantial change in the prevalence of disease [136, 137]. To date, small trials of helminth therapy suggest no benefit for asthma [138] or for rhinitis [139].

Bowel flora

Differences in bowel flora in infants with wheeze and asthma have been reported [140, 141]. In infants, gut microbiota are determined by multiple factors including mode of delivery, type of infant feeding, gestational age, infant hospitalisation and antibiotic use [142]. It has been hypothesised that the higher prevalence of asthma in those born by Caesarean section is due to failure of normal colonisation of the infant gut, which would occur during vaginal delivery [143, 144], and that the strong associations of antibiotic use with increased asthma and hay fever [145] is due to changes in intestinal microbiota. However, correlations with Caesarean section may be confounded by unmeasured fetal and maternal characteristics and associations with antibiotics may arise through reverse causation as children with atopy have more infections and are more likely to be prescribed antibiotics [146].

In 2008, 12 randomised controlled trials of probiotics to treat asthma and rhinitis (hypothesised to exert a protective effect on allergic disease through changes in bowel flora)

were identified [147]. Although the trials differed in many ways (types, forms and quantities of probiotics used in the active arms during treatment duration), the review concluded that probiotics may be of value for treatment of rhinitis; however, there was little consistent evidence for asthma. Probiotics have been investigated as a possible route for primary prevention of disease but results have been disappointing, showing some protective effects for sensitisation and rhinitis but not for asthma [148–150].

Anthroposophic lifestyle

Children bought up following the anthroposophic or Steiner lifestyle have lower prevalence of asthma and hay fever than non-Steiner children living in the same area [151]. This has been attributed to their higher intake of foods containing lactobacilli (and therefore altered bowel flora), lower vaccination rates, lower paracetamol use, lower use of antibiotics and higher consumption of unpasteurised milk [152]. The possible protection afforded by an anthroposophic lifestyle may last into adulthood for rhinitis, but not for asthma [153].

Paracetamol intake

Ecological, multicentre cross-sectional and cohort studies in Europe, Africa and the USA suggest frequent paracetamol intake is associated with asthma in children and adults [154–157] and that paracetamol in late pregnancy may be associated with increased risk of asthma in the offspring [158]. As associations may arise due to confounding by indication, randomised controlled trials are needed to determine whether these associations are causal. One randomised controlled trial has shown that paracetamol compared to ibuprofen may delay recovery from acute asthma in children [159], and another small study of adults with mild-to-moderate asthma suggests paracetamol intake over 12 weeks had no effect on symptoms or airway responsiveness [160].

Farming

There are many cross-sectional studies showing that European children brought up on farms have less wheeze, asthma and hay fever than those who are brought up in the countryside but not on farms [161–163]. Various aspects of farming life have been implicated (maternal exposures during pregnancy, high exposure to endotoxin, high exposure to diverse bacteria and fungi, drinking unpasteurised milk) and not all farming environments have been linked to lower prevalence of disease [163, 164]. More recently the ISAAC study showed that early exposure to farm animals (a proxy for farm living) and maternal exposure to farm animals while pregnant were associated with an increased risk of asthma symptoms and rhinitis in children living in non-affluent countries [165]. In Europe at least, the protective effect of farming for rhinitis may, in some part, last into adult life [166].

Family history

It has long been recognised that asthma and rhinitis "run in families". Genome-wide association studies have identified single nucleotide polymorphisms associated with asthma [167] and rhinitis [168] and atopy [169]. Genetic variants may modify the effect of environmental exposures such as environmental tobacco smoke [170, 171], infections [130]

and farming [172] on asthma risk. The genetics of asthma will be addressed more comprehensively in the chapter by BOEZEN *et al.* [173].

Exposure to allergen

People with asthma and hay fever will often report that their symptoms are triggered by exposure to allergens. Health service utilisation data suggest asthma exacerbations are more frequent when levels of grass pollen and mould spores are high [174–176], and are more likely to occur in those sensitised to the prevalent allergen [177]. Exposure to *Alternaria alternata* in sensitised individuals has been associated with near fatal asthma [178]. Thunderstorms may cause particularly high allergen levels and epidemics of asthma have been reported following thunderstorms [179, 180]. Ambient air may contain other allergens secondary to industrial processes, and asthma epidemics have been attributed to transient acute rises in ambient soy bean, castor bean and other allergens [181–183].

Indoor exposure to house dust mite has been implicated in the development of asthma in some [184] but not all [185, 186] studies. For many years families with children at risk of atopy and asthma have been urged to avoid keeping family pets. There are many studies investigating associations of keeping pets with sensitisation and asthma, but "selective avoidance" by those who are at risk makes interpretation of cross-sectional studies difficult, a problem that is not entirely overcome in longitudinal studies. A recent systematic review of observational studies concluded that although keeping dogs may protect against sensitisation, there was little evidence that exposure to cats or dogs in early childhood influenced the development of asthma [187]. Randomised controlled trials of reductions in indoor allergen exposure show no evidence of benefit for asthma through reduction in house dust mite allergen [188] or cat allergen [189].

Smoking and passive smoking

Adults who smoke are at increased risk of multiple respiratory diseases, but the reported relationship of active smoking with the development of asthma is remarkably inconsistent [190]. These inconsistencies may, in part, be explained by reporting biases, "healthy smoker bias", and whether a highly specific definition of asthma that excludes COPD has been used. Some reports suggest smoking is associated with asthma development [191] and active smoking may increase severity of asthma [192]. There is no evidence that hay fever is more common in adult smokers, and some cross-sectional studies (which are liable to the healthy smoker bias) show that it is less common in smokers [86, 193, 194]. These latter observations are in stark contrast to the strong association of chronic rhinosiniutus with smoking [48].

There is considerable evidence that children of smoking parents have more respiratory illness suggestive of asthma [195], and a review of 79 cohorts examining the incidence of asthma showed a 20% increase in asthma in children living with a smoking mother [196]. The association of prenatal smoke exposure with asthma is seen most clearly in children with a low birth weight [197]. In most studies it is difficult to disentangle the effects of prenatal from post-natal maternal smoking, and maternal from paternal smoking as these exposures are highly correlated. Some of the emerging interest in "transgenerational" transmission of asthma risk was prompted by the observation that children whose grandmothers smoked during their mother's fetal period had more symptoms of asthma, even if their own mothers had not smoked during pregnancy [198].

Marked reductions in childhood asthma admissions have been reported in the year following the introduction of smoking bans in public places reflecting the harmful effects of environmental tobacco smoke [199, 200]. Adults exposed to other peoples' tobacco smoke, particularly in the workplace, have more symptoms suggestive of asthma and more bronchial reactivity [201].

Diet and obesity

The role of maternal and own diet and nutritional status on asthma has been extensively studied. Multiple factors and dietary patterns have been implicated as increasing the risk of asthma (low intake of fruit and vegetables, fish, dairy fat, antioxidants, magnesium, omega-3 fatty acids, and high intake of sodium and omega-6 fatty acids), but the evidence is far from clear [202, 203]. There are few large longitudinal studies with comprehensive dietary assessment and prolonged follow-up, and in the few trials that have been conducted, dietary manipulation has had little effect on disease [204, 205]. A recent extensive narrative review on diet and asthma concluded that future research should be targeted at clarifying the role of "vitamin D for the prevention or treatment of asthma, choline supplementation as an adjuvant treatment for asthma, and vitamin E to prevent the detrimental effects of air pollution in patients with asthma" [206]. The role of breast feeding remains controversial, with observational studies suggesting breast feeding is protective for asthma and large randomised controlled trials suggesting otherwise [207].

People who are fat, particularly females [208, 209], are at an increased risk of asthma, but the association of obesity with rhinitis is less clear [210]. Weight loss has been associated with improvements in asthma even though there is little evidence that there are substantial changes in inflammatory markers typical of the disease [211]. The association of asthma with diet, including diet in early life, and obesity will be addressed in the chapter by Malli *et al.* [212].

Sex hormones

Multiple epidemiological studies show a higher incidence and prevalence of asthma in boys compared to girls [213]. This is not fully explained by sex-related differences in reporting, labelling and treatment of disease [214] and may be related to hormonal differences, as shown by changes in sex differences during pubertal stages, cyclical variation of asthma symptoms with menstrual cycle, and limited evidence that exogenous hormones may influence disease severity. The association of asthma with sex hormones will be addressed in the chapter by Zemp *et al.* [215].

Air pollution

In many communities, increases in asthma and hay fever have occurred over a period when there have been marked increases in traffic-related air pollution. The current evidence of the role of air pollution on health, including the inception and exacerbation of asthma, has been comprehensively reviewed through a recent initiative from the World Health Organization [216, 217]. Time series studies of asthma mortality and asthma admissions, and panel studies of those with established disease suggest it has a role to play in asthma exacerbations [218]. The recent ESCAPE study which incorporated information from major European cohorts on asthma and annual average residential pollution levels has presented data suggesting no association of main pollutants with asthma incidence in adults, but at the time of writing is

yet to publish their final results [219]. The association of asthma and rhinitis with air pollution will be addressed in the chapter by SIMONI [220].

Conclusion

This summary of current knowledge on the epidemiology of asthma and rhinitis highlights the major fields of research and cannot address all complexities of epidemiological research in this area. A range of risk factors have been explored, but this extensive research effort has not yet led to clear and unambiguous public health policies for the prevention of disease other than those that would be in place for good general health (avoidance of smoking, maintenance of normal body weight and balanced diet). As both asthma and rhinitis are common and are likely to increase globally as populations become increasingly urbanised, further investment in large scale epidemiological studies with deep phenotyping and extensive exposure assessment remains a priority.

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Tuberculosis

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TB is an infectious disease caused by strains of *Mycobacterium tuberculosis*. It is one of the most important diseases worldwide, together with malaria and HIV/AIDS. The last World Health Organization report highlighted an estimated global incidence of 8.6 million cases (*i.e.* 122 cases per 100 000 population) in 2012; the highest figures were estimated in India, China, South Africa, Indonesia and Pakistan. In the majority of the cases, high-income countries show an estimated incidence <10 patients per 100 000 population. HIV/AIDS plays an important role in the development of TB disease; consequently, geographical areas characterised by an high HIV/AIDS prevalence show a high TB incidence. Disorders which impair the immune system (*e.g.* diabetes mellitus or exposure to immunosuppressive drugs) favour the occurrence of pulmonary and/or extrapulmonary forms of TB. A new World Health Organization public health strategy has been recently launched to reduce the global incidence to less than one TB case per 100 000 population by 2050.

TB is a serious airborne disease caused by a bacterial agent, named *Mycobacterium tuberculosis* [1]. The disease represents one of the clinical outcomes related to the infection. However, the epidemiology of this bacterial infection is complex and not completely understood. Numerous mycobacterial, host and environmental factors can influence the transmission and acquisition of the infection, its latency, the clinical evolution into pulmonary and extrapulmonary forms, or, in case of severe and/or untreated disease, its progression to death (fig. 1) [2].

The global scenario

TB, together with HIV/AIDS and malaria, represents an important clinical and public health priority worldwide [3–6]. The administration of anti-TB antibiotics alone has proven to be inefficient as a radical solution to *M. tuberculosis* infection and its most relevant clinical outcomes, *i.e.* the pulmonary and/or extrapulmonary disease. It is thought that a comprehensive public health approach may have a significant effect on the elimination of TB worldwide [7–10].

The most recent World Health Organization (WHO) global report on TB, issued in 2013, pointed out a critical situation globally, particularly in low- and middle-income countries [11]. The impact of TB is summarised by three epidemiological indicators: incidence,

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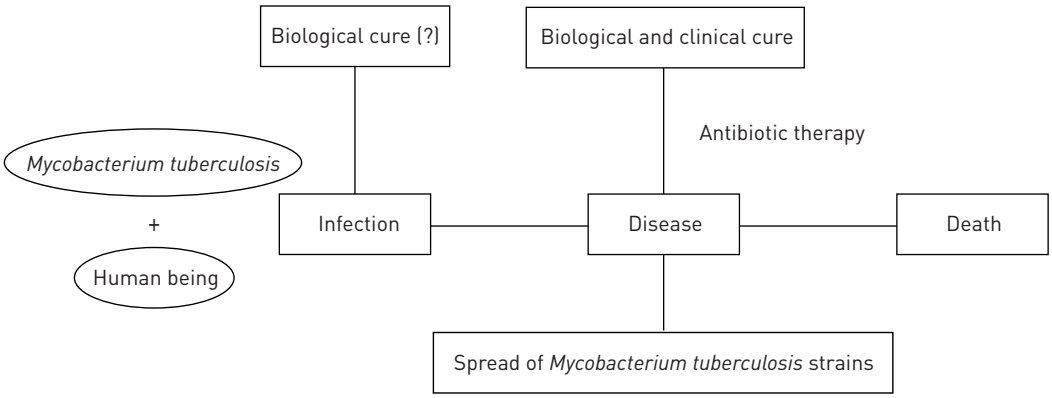

Figure 1. Natural history of TB.

prevalence and mortality. However, the TB phenomenon is complex and several demographic (*e.g.* age, sex, race and geographical area), clinical (*e.g.* HIV/AIDS, diabetes mellitus and silicosis) and epidemiological (*e.g.* type and time of exposure) variables should be taken into account in order to cover all of the public health issues and to organise adequate preventive measures [2].

Furthermore, the epidemiological methods currently adopted by national public health systems show relevant shortcomings, particularly in low-income countries, reducing both the quality of data and the reliability of indicators. The most critical consequence is that, without adequate ability to frame the epidemiological impact and the potential interventions, economic resources, including the human workforce, will not be appropriately allocated. The WHO has adopted methodological countermeasures to bypass these knowledge gaps, and issues trustworthy estimates every year.

The TB incidence is significantly different when compared with the notification rate, particularly where the proportion of patients notified by surveillance systems is low. The under-reporting could be caused by patient- and/or healthcare-related pitfalls.

The incident burden was substantial in 2012, although less than the estimates computed in the past: 8.6 million (range 8.3–9.0 million) new cases were diagnosed worldwide, with a rate of 122 patients per 100 000 population [11]. The WHO Asian (South-east Asia and Western Pacific regions) and African regions had an important proportional contribution, equivalent to 85% of the total incidence (58% and 27%, respectively); percentages were less than 10% in the other regions (Eastern Mediterranean 8%, European 4%, and American 3%) (fig. 2) [11].

It has been calculated that 12–14% of the total incident cases had TB/HIV co-infection, *i.e.* 1.1 million (range 1.0–1.2 million) [11]. The main location of patients with TB/HIV co-infection is in the African region, where, particularly in the sub-Saharan area, the HIV/AIDS epidemic has been catastrophic since the 1980s.

The countries with the highest incident estimates for TB are India (range 2.0–2.4 million), China (range 900 000–1.1 million), South Africa (range 400 000–600 000), Indonesia (range 400 000–500 000) and Pakistan (range 300 000–500 000) [11]. These incident estimates are strikingly different if compared with those computed in the USA, Canada, Australia, New

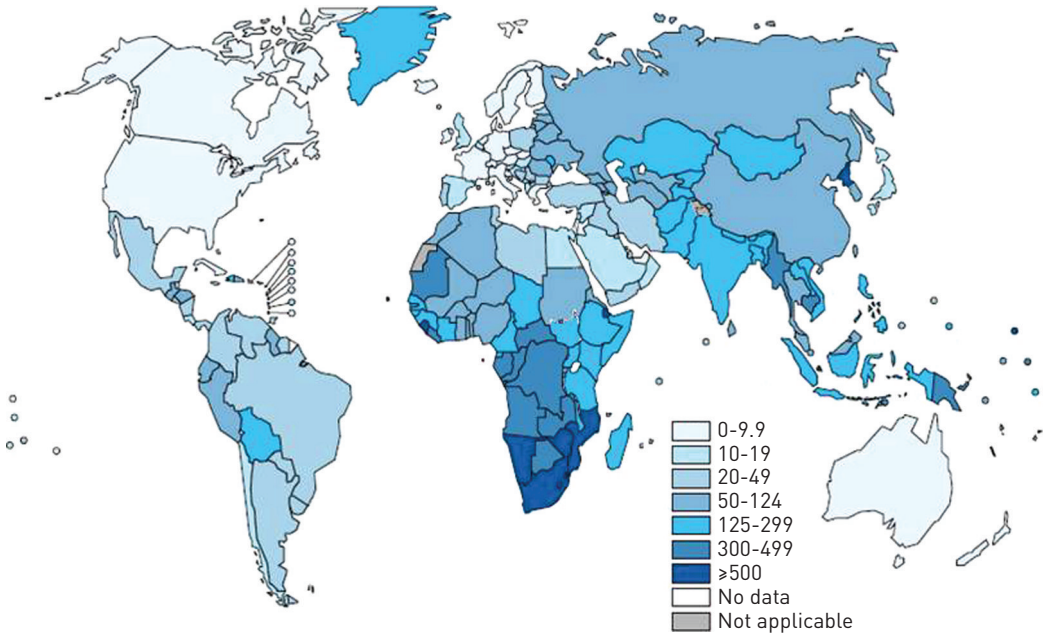

Figure 2. Estimated global TB incidence rate per 100 000 population per year, 2012. Reproduced and modified from [11] with permission from the publisher.

Zealand and European countries, where the characteristic incidence rates were <10 per 100 000 [11]. However, in some cities, where the migration rate from high-burden countries is striking (*e.g.* London in the UK), the incidence was higher than 20 per 100 000 population. The worst incidence rates (*i.e.* >500 per 100 000 inhabitants) were recorded in African countries, such as Mozambique, South Africa, Swaziland and Zimbabwe [11].

Another striking finding outlined in the most recent WHO report [11] is the incidence of TB in children (about 500 000 new cases in 2012). It is likely that numerous patients are not notified because of the diagnostic difficulties of obtaining sputum samples during childhood.

The male-to-female ratio is greater than 1 (*i.e.* an incidence of 2.9 million in women); the sex imbalance can be explained by several sociocultural and demographic factors, particularly in some Asian and African countries.

The slow decrease in TB incidence over the past three decades was related not only to the HIV/AIDS epidemic but also to drug-resistant forms of pulmonary and/or extrapulmonary TB. Multidrug-resistant TB (MDR-TB), which is TB caused by *M. tuberculosis* resistant to at least two of the most potent anti-TB drugs, isoniazid and rifampicin, has caused several clinical and public health issues. The few expensive and less efficacious anti-TB drug choices have not helped to reduce the infectivity of MDR-TB patients, favouring *M. tuberculosis* transmission in the community. It was estimated that 450 000 (range 300 000–600 000) new patients acquired MDR-TB in 2012 [11]. However, at the beginning of the past decade, after a plateau of global TB incidence rate, an annual rate of decline of 2% was recorded, with significant variability between the WHO regions (from less than 1% in the Eastern Mediterranean region to 6.5% in the European region) [11].

TB prevalence was estimated to be 12 million (range 11 million–13 million) cases globally in 2012, which is 169 patients per 100 000 population [11]. Worldwide an annual decline in prevalence has been recorded since 1990. The total decline has been 37% since 1990, with different epidemiological scenarios in the WHO regions (prevalence has halved if compared with that in 1990 in the American and Western Pacific regions; whereas estimates of decline in the African and Eastern Mediterranean regions are negative) [11].

Evaluation of the national prevalence data is complicated because it could be obtained by selecting large sample sizes in specific surveys, which are expensive, or, alternatively, by using the incidence and the mean duration of TB disease in a specific setting.

Another important epidemiological indicator is mortality. In 2012, 1.3 million people died of TB, which is equivalent to 13 per 100 000 population: the majority of them were HIV negative (*i.e.* 940 000) [11]. About two-thirds of the deaths were recorded in the African and South-East Asian WHO regions, where South Africa and India played an important role. The trend for annual decline was positive, with a fall of 45% when mortality estimates were compared with those calculated in 1990 (fig. 3) [11].

Natural history of TB

TB is a disease that results from an infectious process caused by strains of *M. tuberculosis* [12]. The interaction model between bacterial strains and humans is not deterministic but probabilistic: the probability of developing the infectious disease depends on the relevance of known and unknown variables. Knowledge about specific variables allows quantification of the probability of the clinical outcomes.

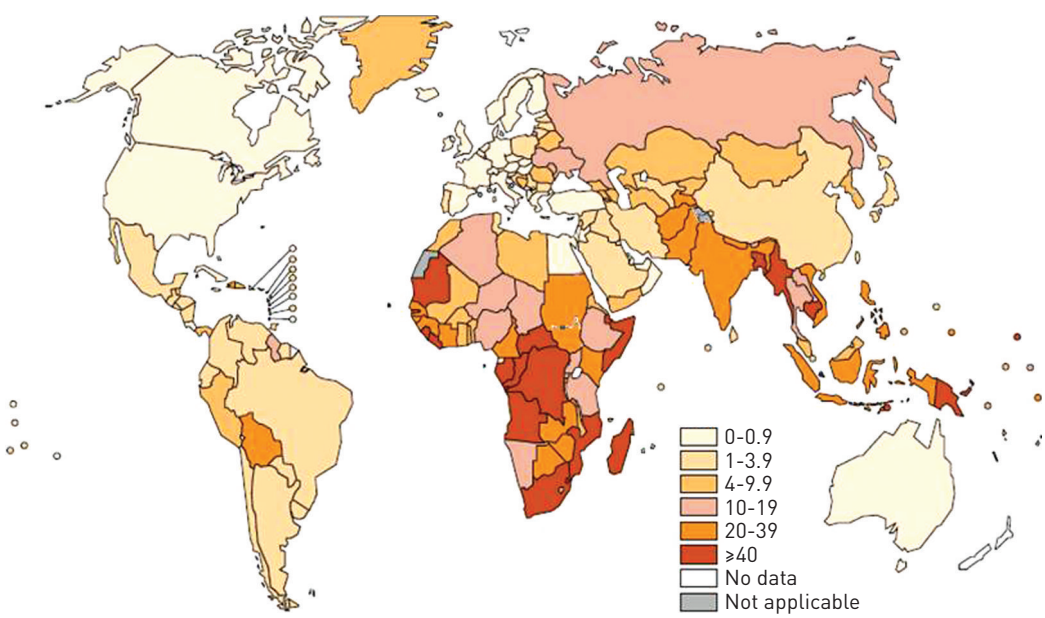

Figure 3. Estimated global TB mortality rate per 100 000 population, 2012. Reproduced and modified from [11] with permission from the publisher.

The potential outcomes of the bacterium–human interaction are: latent TB infection (LTBI); pulmonary and/or extrapulmonary forms of TB disease; and death. Variables related to the biological agent, to the host and to the environment could play an additive or a synergistic role in the development of the above mentioned clinical effect [2, 12, 13].

The first crucial step in the infectious chain, which is responsible for the disastrous global epidemiological indicators, is the exposure of a noninfected individual to an index contagious patient (*i.e.* a case affected by a pulmonary form), who spreads mycobacteria in the environment by coughing, sneezing, singing or talking. Even if it is not possible to quantify the risk of exposure, several authors agree that critical exposure occurs in a small environment with poor ventilation, over the course of several hours ($>$8 h is considered a potential cut-off) [2]. The bacterial load of the index patient could be important: it has been shown that individuals who are sputum smear positive ($\geqslant$5000 mycobacteria in 1 mL) and culture positive are more contagious than those who are sputum smear negative and culture positive. The latter are more infectious than those who are sputum smear negative and culture negative [2].

The probability of being infected depends on the frequency of the prevalent cases. The size of the pool of contagious prevalent cases is strictly linked to the incidence of the disease in a specific setting and to the duration of infectiousness of the patients. The number of incident cases is mainly associated with host characteristics (*i.e.* innate and acquired immunity) and, indirectly, with the intensive circulation of *M. tuberculosis* strains.

The duration of infectiousness can be associated with patient and/or healthcare system factors. Early detection and treatment of the contagious patient can reduce the probability of *M. tuberculosis* transmission. A sputum smear positive patient can infect an average of 10–12 contacts annually. Causes of delayed diagnosis are recognised to involve both patient and healthcare system factors: alcohol or drug abuse, stigma, poverty, poorly trained physicians, sputum smear and/or culture negativity, poor capacity of the laboratory, *etc*. Individuals with a pulmonary form of TB should be admitted to a ventilated (11 air changes per hour for a 24 m^3 room) isolation room, with a negative pressure. Antibiotic therapy should be prescribed immediately but should be tailored based on the drug susceptibility testing results [2, 7, 14]. A combination of efficacious drugs, prescribed for a long period of time, with adequate dosages, can reduce the bacterial load and may mean the patient can be discharged from the isolation room. Unfortunately, the microbiological results, including those related to culture and drug susceptibility testing, can take more than 1 month to obtain. Consequently, it is usual to prescribe an empirical antibiotic regimen, which can fail in cases of resistance to one or more antibiotics; on this basis, the duration of infectiousness can increase, with a risk for the attending healthcare workers if they are not adequately protected. Geographical areas in which the prevalence of MDR-TB cases is high are at an increased risk of failing the empirical regimen [2, 11].

After discharge, patients should be strictly followed-up in the community during their treatment, by nurses, social workers or trained family members, because adherence to the prescribed anti-TB regimen is crucial to avoid subtherapeutic drug levels in the blood. Directly observed treatment is strongly recommended, together with a clinical follow-up to evaluate the occurrence of adverse events, which can reduce patients' adherence. In poor countries/geographical areas, reduced adherence can be related to the patients' inability to reach the medical centre to take their medication: the location is too far away (*e.g.* individuals live in rural areas), the cost of public transport is too high, or the risk of becoming unemployed hinders treatment continuity. Furthermore, the stigma following the diagnosis

of TB should be taken into account. From this perspective, attending a TB centre could be considered socially dangerous and, thus, "force" the patient to interrupt their drug intake.

Demographic and social factors can increase the risk of exposure to TB patients. Crowded locations can be a risk (*e.g.* cities and small houses with a high inhabitant density); in general, the size of the population, particularly in cities, can increase the probability of being infected. In some countries, social activities can differ by sex and, consequently, produce sex-specific exposure to index cases. Another important issue is the mean age of TB patients. In low-incidence countries, the elderly tend to develop TB after acquiring the infection during childhood. As a result, children living with their grandfather and/or grandmother could have a high chance of acquiring infection and of developing TB disease [2, 15, 16].

Environmental and meteorological factors could also influence social relationships: in geographical areas characterised by warm temperatures, the probability of indoor contacts decreases. Moreover, the role of solar ultraviolet radiation in killing *M. tuberculosis* strains is well known.

After a critical exposure and the inhalation of the droplet nuclei from a sneezing, coughing, talking or singing TB patient, both mycobacterial and host variables are crucial in the development of the infectious process.

Particles containing mycobacteria that have a diameter of 1–5 μm can be inhaled and reach the pulmonary alveolar spaces. The probability of being infected is related to mycobacterial load; it can be decreased using a ventilation system in the environment (natural, mechanical or mixed mode natural/mechanical). However, in order to understand the efficacy of ventilation interventions it is important to carry out an environmental study (direction of the natural ventilation, characteristics of the building, number and location of the windows, meteorological expectations during the year). When mechanical ventilation is in place, it should be maintained by engineers. In isolation rooms, the mechanical ventilation is frequently associated with ultraviolet germicidal irradiation devices. By contrast, when the patient is at home, natural ventilation should be studied and individuals in the household should decrease their contact frequency and should use personal protective equipment (*i.e.* particulate air-filter respirators N95/N99 or FFP2/FFP3 to specifically to block droplet nuclei sized 1–5 μm); in addition, patients, and not contacts, should wear surgical masks. Cough etiquette and health education activities at home and in the community can reduce the probability of being infected, decreasing exposure and stigma. Healthcare workers employed in high-risk departments or services should evaluate the efficacy of respirators by performing fit-testing (*i.e.* no leakages near the nose and the mouth) [17].

Once infected, in the majority of cases individuals develop a subclinical state, which can currently only be diagnosed indirectly, by assessing adaptive immunity against *M. tuberculosis* antigens. The WHO estimates that about 2 billion individuals are infected by *M. tuberculosis*. Two diagnostic techniques can be performed: tuberculin skin testing and interferon-γ release assay. Their diagnostic accuracy is less than 95% for the identification of LTBI and for TB disease. Tuberculin skin testing, based on intradermal injection of a purified protein derivative collected after filtration of a *M. tuberculosis* culture, is characterised by several shortcomings: among them the cross-reactivity between *M. tuberculosis*, nontuberculous mycobacteria and BCG antigens should be noted. Furthermore, the test should be performed by a trained healthcare worker in a two-step process and the reaction (*i.e.* an intradermal induration) should be read and interpreted, taking into account several variables, such as a severe immune deficiency [2, 13].

Interferon-γ release assay, based on the collection of a few millilitres of blood, is more specific, because the two current commercial versions (QuantiFERON-TB Gold In-Tube assay (QFT-GIT), Cellestis Ltd., Melbourne, Australia; and T-SPOT-TB, Oxford Immunotec, Abingdon, UK) contain *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). A long and interesting debate has not solved the diagnostic dilemmas of the two techniques, in particular their applications, the target, the timing, and their diagnostic accuracy in several clinical conditions [18].

Innate (mainly antigen-presenting cells and macrophages) and adaptive immunity (T- and B-lymphocytes) are crucial in the control of the replication of mycobacteria in the lungs. Several authors have debated whether a biological cure can occur after the infection process starts; the qualitative and/or quantitative deficiency of the innate and/or acquired immunity can favour an increase in the replication rate and, consequently, relevant pulmonary pathological alterations [19, 20].

The probability of developing the disease is elevated in the first 2 years after mycobacterial exposure and infection (5%); after 5 years, it is estimated that the probability is lower than 5%. However, the risk can be significantly high when the infection is acquired during childhood. Impaired immunity in children can explain this epidemiological hazard [2].

Several comorbidities that alter the immunological network increase the risk of TB disease. One of the most important is HIV/AIDS. The annual risk of disease is 5–15% when the *M. tuberculosis* infection was acquired before the HIV infection. A higher risk is estimated in cases of a secondary *M. tuberculosis* infection. The most important pathological feature of the HIV infection is the qualitative and quantitative impairment of $CD4^+$ lymphocytes, which are a cornerstone of the host response to mycobacteria, as shown in several experimental studies [2, 21, 22]. Administration of isoniazid (isoniazid preventive therapy) and of antiretrovirals can reduce the probability of developing TB disease [2, 21, 22].

Diabetes mellitus, which has a high prevalence and incidence in several geographical areas, increases the risk of developing TB disease by 1.5–8 fold. An abnormal response of the innate and adaptive immunity can favour an increase in mycobacterial replication [2, 23, 24]. More than 80% of diabetic patients live in low- and middle-income countries where TB incidence is high. It is estimated that about 600 million individuals will be diabetic by 2035; this could represent a dramatic risk for a new epidemic [25, 26].

Other clinical conditions at high risk are: chronic renal failure, silicosis, smoking, exposure to immunosuppressive drugs for rheumatic, immunological, and gastro-intestinal diseases, malnutrition, cancer, drug and alcohol abuse, gastrectomy, and jejunoileal bypass [2, 27–30]. The common denominator is immune deficiency, which can include innate and/or adaptive immunity (B- and/or T-lymphocytes). Unfortunately, some of these clinical conditions only

TABLE 1. The elements of the directly observed therapy short course strategy

1. Secure political commitment toward TB, with adequate and continuous financing
2. Ensure early case detection and diagnosis through quality-assured bacteriology
3. Provide standardised treatment with supervision and patient support
4. Ensure effective drug supply and management
5. Monitor and evaluate performance and impact

partially improve after the administration of drugs and, consequently, the risk of developing TB continues to be high when compared with the lifetime risk estimated in the general population. More attention should be focused on these vulnerable groups, particularly in improving collaborative activities between the specific national programmes. Prevention will be crucial. Preventive therapy should be considered after careful assessment of TB risk, according to the severity of the immune deficiency. Noncommunicable diseases will represent a relevant priority in the near future, not only in developed countries but, mainly, in low-income countries, whose healthcare systems may be poorly prepared to combat new epidemiological scenarios [9, 31, 32].

Adequate management of the above mentioned conditions can be helpful in the control of TB disease treated with an adequate antibiotic combination. In cases of delayed diagnosis and/or inadequate treatment mortality can increase.

Public health interventions

TB is an airborne infectious disease whose incidence cannot be decreased by clinical management of existing pulmonary and extrapulmonary cases alone.

It is clear that infectious cases should be clinically treated to reduce the spread of *M. tuberculosis* strains to other individuals; however, a preventive therapy for latently infected cases is mandatory to decrease the number of potential new cases. Unfortunately, this is not an easy task: one-third of the global population is infected and, currently, the diagnostic tools used to assess subclinical infection are characterised by a poor diagnostic accuracy.

It is necessary to prepare, implement and scale-up a global strategy. The WHO has planned and supported the implementation of efficacious strategies since the 1990s [33, 34]. Two strategies were prepared in 1996, directly observed therapy short course (DOTS) and 2006, the Stop TB Strategy. The former mainly focuses on the identification and treatment of infectious TB cases. It is comprehensive and is characterised by five points (table 1).

The national implementation of the DOTS strategy implied two objectives: the detection of 70% of those who are sputum smear positive and the successful treatment of 85% of those detected by 2005 [33].

In 2006, the Stop TB strategy, which took into account new epidemiological scenarios (*i.e.* the global emergence and spread of MDR-TB, and of TB/HIV co-infection), included elements to support the successful DOTS strategy (table 2) [34].

TABLE 2. The elements of the Stop TB Strategy

Pursue high-quality directly observed therapy short course expansion and enhancement
Address TB/HIV co-infection, multidrug-resistant TB, and the needs of poor and vulnerable populations
Contribute to the strengthening of health systems
Engage all care providers
Empower people with TB and communities through partnership
Enable and promote research

In May 2014, the global WHO strategy focused on TB elimination by 2050 (*i.e.* an incidence of less than 1 TB case per million inhabitants) was launched to dramatically improve the epidemiological scenario [3, 35]. The three main pillars of this strategy are summarised in table 3 [36].

Conclusion

TB, an ancient disease, still represents a first-class clinical and public health priority. History has demonstrated that its management should be comprehensive and not only focused on clinical management of infectious cases. Due to the dynamic interaction of numerous variables (from exposure to *M. tuberculosis* to possible death), the epidemiology of TB is complex. On this basis, several stakeholders, including governments and policymakers, clinicians, patients and their communities, donors and international organisations should support the strategic plans that exist at a national and a regional level.

New efforts should be focused on the prevalent pool of latently infected individuals, which are the main source of future incident TB cases.

The epidemiological study of *M. tuberculosis* infection should focus not only on the estimated epidemiological indicators but also on the risk factors that play a role in the natural history of infection.

New diagnostic, therapeutic and preventive tools are needed in the near future to improve the current scenario. Research and socioeconomic development should be the cornerstone of future international projects to fight this evergreen disease.

TABLE 3. The three pillars of the post-2015 World Health Organization strategy

1. Integrated, patient-centred care and prevention
Early diagnosis of TB, including universal drug-susceptibility testing; systematic screening of contacts and high-risk groups
Treatment of all individuals with TB, including those with drug-resistant TB; patient support
Collaborative TB/HIV activities; management of comorbidities
Preventive treatment of persons at high TB risk; vaccination against *Mycobacterium tuberculosis* infection
2. Bold policies and supportive systems
Political commitment accompanied by adequate resources for TB care and prevention
Engagement of communities, civil society organisations, and public and private care providers
A universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of drugs; implementation and scale-up of infection control activities
Social protection, poverty alleviation and action on other determinants of TB
3. Intensified research and innovation
Discovery, development and rapid uptake of new tools, interventions and strategies
Research to optimise implementation and impact, and promote innovations

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Chapter 4

Lung cancer and pleural mesothelioma

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Overall lung cancer incidence increased steadily during the second half of the 20th century, reaching the highest rank among all cancers for both the whole population and age-standardised population worldwide. Today, lung cancer is the leading cause of cancer mortality in many regions. Its major causative agents have been clearly identified over the last six decades, with more than 80% being attributable to cigarette smoking, which makes lung cancer one of the most preventable tumours. In males, the effect of smoking still determines the high risk of dying from lung cancer in industrialised countries, although incidence and mortality have shown a trend to decline among younger generations. In contrast, females in developed and developing countries have similar morbidity and mortality levels; however, given the increasing number of females who smoke, these are likely to grow worldwide.

Pleural mesothelioma is a highly lethal tumour that is much less frequent, except among subjects exposed to occupational or environmental asbestos and asbestos-like fibres. The global burden of mesothelioma is unclear, but its age-standardised mortality rate has doubled during the last two decades.

Cancer is a major public health problem in Europe and in many other parts of the world, including the USA. The gradual decline of once common fatal infections, as well as of noncommunicable serious disorders such as coronary heart disease and stroke, has been paralleled by the increasing risk of an individual developing cancer during his or her life. Among all types of solid tumours, lung cancer is a strikingly important cause of global morbidity and mortality in humans. In addition, the pleura of susceptible individuals exposed to asbestos or asbestos-like mineral fibres may develop malignant mesothelioma, a relatively uncommon and yet incurable tumour that is aggressive and highly lethal. The importance of these tumours stems from either the relentless increase in their incidence during the last hundred years or, even more disconcerting, the huge number of individuals that succumb to their occurrence. According to current knowledge, every year more than 1.5 million people die from lung cancer worldwide. Thus, lung cancer alone causes more deaths than the next three most common cancers (*i.e.* colorectal, prostate and breast cancer) combined [1]. This

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devastating situation has arisen not only from the elimination of other diseases and the subsequent lengthening of lifespan but also from the increasing exposure to numerous agents, including cigarette smoke and other air pollutants, which have turned out to be carcinogenic for the respiratory system.

A huge bulk of studies have contributed significantly to our current knowledge of the epidemiology of pulmonary and pleural neoplasms in Europe and worldwide. During the last six to seven decades, the epidemiological approach has been successfully used not only to assess the frequency, sex and age distribution of these tumours, but also to characterise their natural history and to identify their determinants and disease mechanisms. Several comprehensive review articles providing consistent and updated epidemiological data on lung cancer and pleural mesothelioma are published each year [2–5].

In the present chapter, a brief overview of the epidemiology of lung cancer and malignant pleural mesothelioma is given, with special emphasis on their incidence and mortality in Europe as well as on their pathogenesis, which is amenable to a number of both non-occupational and occupational risk factors.

Lung cancer

The term "lung cancer" includes a group of specific malignancies of the lung with different histological appearance. The current classification system can be summarised into three main histological patterns: 1) small cell carcinoma, 2) large cell carcinoma, and 3) nonsmall cell lung carcinomas, including either adenocarcinoma or squamous cell carcinoma and their histological subtypes. Lung cancer has a very high incidence and mortality rate worldwide but it is also the most avoidable of all cancers, as over 80% of cases are attributed to cigarette smoking. Lung cancer was a rare diagnosis in the 19th century, but it started to increase in the first two decades of the 20th century. Thereafter, its incidence and mortality have steadily increased as the result of spreading of smoking throughout the world. Thus, in the past 100 years, lung cancer has shifted from a rare disease into a global public health problem. At the beginning of the 20th century, the malignancy was recognised as primary carcinoma of the lung [6, 7]. In the 1930s, with the increasing incidence of lung cancer in the general population, its pathogenesis was reviewed and it was concluded that cigarette smoke was the causative agent of lung cancer [8]. Thereafter, DOLL and HILL [9] described mounting evidence that lung cancer was associated with cigarette smoking, and subsequently the Royal College of Physicians in the UK and the Surgeon General of the USA firmly established its causal relationship with smoking [10, 11].

Although the epidemiology of lung cancer has been extensively investigated in the last six decades, there is still substantial interest in this field, with special efforts aimed at identifying aspects that may be relevant to prevention and early diagnosis and to the recognition of pathogenic *noxae* different from tobacco smoking. Thus, several studies have been carried out to investigate the genetic susceptibility to lung cancer or its association to diet and a number of other risk factors, including indoor air pollution from biomass, gas cooking or house heating. Increasing concern has been expressed over the risk of outdoor pollutants, including radon and diesel exhaust. Moreover, the current evidence indicates that the combination of these factors and that of cigarette smoking may have synergistic effects over time. Finally, there is also emerging evidence on the genetic determinants of lung cancer risk [12].

Incidence

Lung cancer is a global leading cause of morbidity, with about 1.8 million new cases estimated in 2012; 1.2 million cases in males and 0.6 million in females, corresponding to nearly 66% and 34%, respectively, and accounting for 12.9% of all new cancers worldwide [1]. Lung cancer is the most commonly diagnosed cancer worldwide, but its global geographic distribution shows marked regional differences: the highest incidence rates are observed in East Asia and Europe (22.9% and 15.9% of all cancers, respectively). Differences are registered between high- and low-income countries (14.1% and 6.7% of all cancers, respectively). Lung cancer tends to be more frequent in industrialised regions such as Europe and North America and less common in less developed areas such as Africa and South America [4]. Lung cancer is the most common malignancy in males and the third most frequent in females (16.7% and 8.8% of all cancers, respectively) worldwide. The global incidence rates of lung cancer in females are lower than in males. However, it is noteworthy that female lung cancer incidence has steadily increased in the last few decades, and it has been recently reported that lung cancer reached third place in the global ranking, overtaking cancer of uterus [1]. Thus, in the USA, the incidence over the past 36 years has dropped for males (24% decrease), while it has risen for females (100% increase). In 1984, the rate of new cases for males peaked (102.1 per 100 000) and then began declining, reaching 44 cases per 100 000 in 2012. The rate of new cases for females increased until it reached a peak in 1998 (52.9 per 100 000) and has then started to decline, with recent data calculated to be 34 per 100 000 in 2012. It is likely that this trend reflects a change of smoking habits, with smoking becoming slightly less prevalent in males while increasing in females [13].

In 2012, lung cancer was one of the most common cancers in the World Health Organization (WHO) Europe region, being responsible for about 450 000 new diagnoses, corresponding to 11.9% of all cancers and occupying one of the highest ranking places together with cancer of the breast, colorectum and prostate. It is estimated that the age-standardised incidence is 23.1 per 100 000 worldwide and 29.0 in Europe (WHO Europe region), with significant difference between males and females (46.6 and 15.1 per 100 000 per year, respectively). In the European Union (28 member states (EU-28)), the age-standardised incidence is approximately 30 cases per 100 000 population. In general, age-standardised incidence rates for males, but not for females, are greater than those estimated by both-sex analysis. Thus, in males, the estimated incidence rates are 46.6 and 45.1 per 100 000 in Europe and EU-28, respectively. 10 of the 15 countries with male rates higher than the European average are located in Central and Eastern Europe. Figure 1 shows 20 countries with the highest age-standardised (world population) incidence and mortality rates for male and female subjects in Europe. In males, the highest incidence rates are seen in Hungary (76.6 per 100 000 males), Macedonia (71.3), Serbia (70.3) and Montenegro (62.4). In females, incidence is higher in Denmark (37.6 per 100 000 females), Hungary (33.2), the Netherlands (31.6) and Ireland (27.4). These figures point out that much remains to be done to prevent, cure and relieve suffering from lung cancer worldwide.

Mortality and 5-year survival rates

Lung cancer is the most common cause of death from cancer worldwide. It is estimated to be responsible for 1.6 million deaths per year, corresponding to nearly one in five cancer deaths. Lung cancer is not only the biggest cancer killer in North America and Europe, accounting for the largest number of cancer deaths among males in all Organisation for Economic Co-operation and Development countries (except Sweden and Iceland), it is also one of the

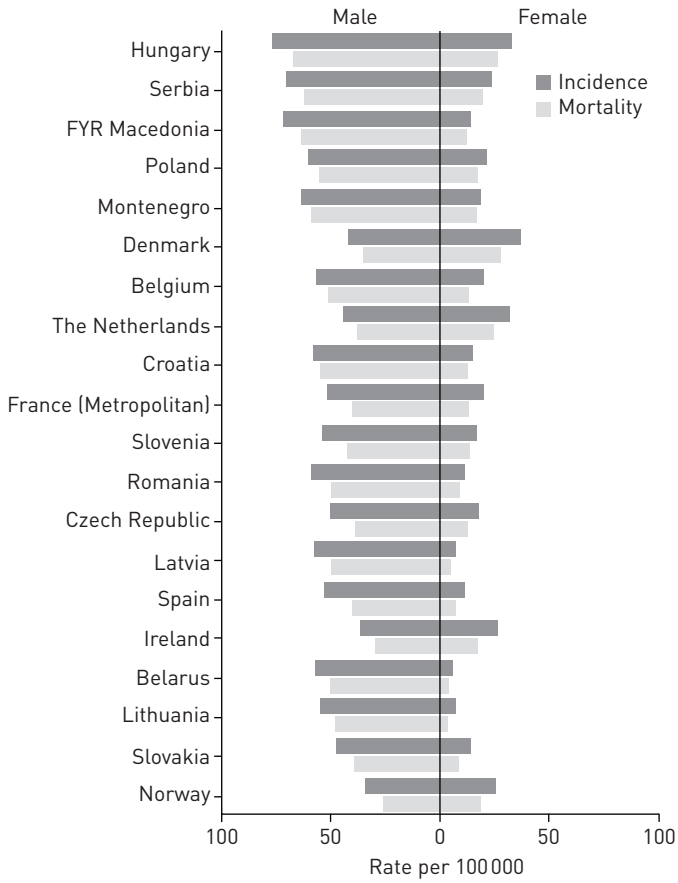

Figure 1. Age-standardised (world population) rates of lung cancer incidence and mortality in both sexes for the 20 European countries with the highest rates. Reproduced and modified from [1,14] with permission from the publisher.

main causes of cancer mortality among females. The overall ratio of mortality to incidence for lung cancer in Europe in 2012 was 0.86; this value is higher than the mortality to incidence ratio for all cancers (roughly 0.50) and other highly prevalent cancers as well (table 1). This emphasises the higher fatality and worse prognosis of lung cancer compared to other tumours. In addition, due to the relative lack of survival variability in different European countries, the geographical patterns of mortality closely reflect those of incidence (fig. 2) [1].

The GLOBOCAN 2012 fact sheets for population report 350 000 deaths from lung cancer in Europe (250 000 males), corresponding to 20% of total deaths from cancer, and age-standardised death rates of 26.1 per 100 000 males and 11.8 per 100 000 females [1]. Interestingly, the age-standardised death rates in the 1990s in Europe were 50.3 per 100 000 and 10 per 100 000 in males and females, respectively [1].

Tobacco smoking is the most important risk factor for lung cancer. In 2008, death rates from lung cancer among males were the highest in central and eastern European countries (Hungary, Poland, Estonia, Latvia, Lithuania and others). These are countries where smoking rates among males are relatively high. Death rates from lung cancer among males are low in

Table 1. Estimated new cases, deaths, deaths to cases ratio and 5-year prevalence for lung cancer, breast cancer, prostate cancer and colorectum cancer worldwide and in Europe in 2012

	Worldwide				Europe			
	Cases	Deaths	Ratio#	5-year prevalence	Cases	Deaths	Ratio#	5-year prevalence
Lung cancer	1825	1590	0.87	1893	449	388	0.86	476
Breast cancer	1677	522	0.31	6255	500	143	0.29	1960
Prostate cancer	1112	307	0.28	3924	437	101	0.23	1579
Colorectum cancer	1361	694	0.51	3544	471	228	0.48	1258

Data are presented as estimated numbers ×1000, unless otherwise stated. The prevalence data are from the year 2008 [14]. #: ratio of mortality to incidence. Reproduced and modified from [1, 14] with permission from the publisher.

Sweden, Iceland, Finland, Norway and Cyprus, where smoking rates among males are low. Denmark and Iceland, however, have high rates of lung cancer mortality among females, suggesting that lung cancer risk increases with quantity and duration of cigarette consumption [1, 5, 9].

The estimated 5-year "limited duration prevalence" (better known as "5-year prevalence") refers to the number of people still alive 5 years from the diagnosis of lung cancer. This prevalence varies according to the sex and geographical patterns of incidence rates. According to the GLOBOCAN report, in 2008 the 5-year prevalence of lung cancer accounted for roughly 1.9 million cases worldwide, corresponding to 5.8% of all neoplastic

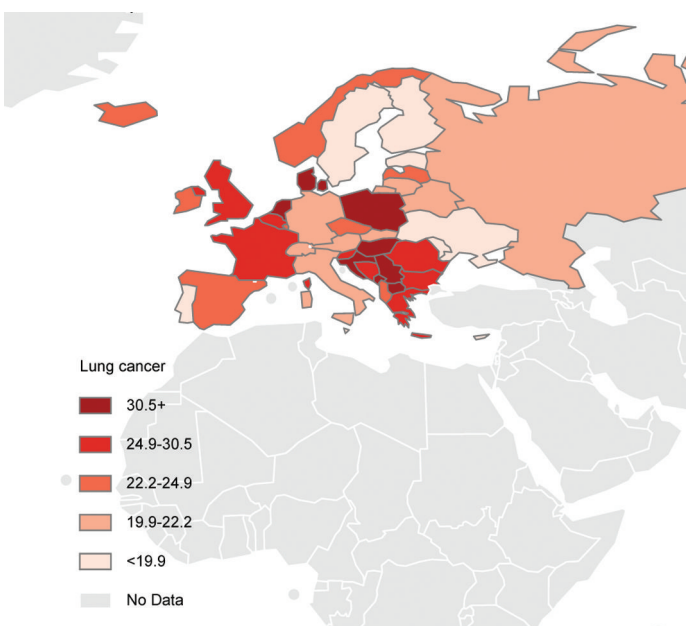

Figure 2. Simplified map of age-standardised (world population) mortality rates for lung cancer in both sexes (all ages). Reproduced and modified from [1,14] with permission from the publisher.

subjects. The higher 5-year prevalence for breast cancer (6.2 million), prostate cancer (3.9 million) and colorectum cancer (3.5 million) worldwide discloses the relatively lower probability of subjects with lung cancer to survive at 5 years after diagnosis (table 1) [14].

In Europe, the estimated 5-year prevalence of lung cancer is 476 000 subjects (343 000 males). This means that only 4.8% of all cancer patients (6.9% among males) have the probability of surviving 5 years after diagnosis. Among females, the 5-year prevalence of lung cancer in Europe accounts for about 133 000 cases (2.8% of all cancers) [14]. A number of factors may contribute to the low rates of 5-year survival, including delay in seeking medical attention and the advanced stage of lung cancer at diagnosis.

Temporal trends

Cases of and deaths from lung cancer have increased constantly in industrialised countries during the last few decades, largely because of the increasing smoking epidemic. Studies have shown that the long-term trends of the age-adjusted incidence rates in both males and females are consistent with the spreading pattern of tobacco use.

Using the mortality rates for lung cancer and population data of the WHO Statistical Information System, Malvezzi *et al.* [15] calculated the number of deaths from all cancers and cancers of selected sites for the European Union (EU-28) and six major European countries, by fitting a joinpoint model to 5-year age-specific numbers of deaths, and estimated rates for 2014. They used the official death certificates to collect data for cancer of the stomach, colorectum, pancreas, lung, breast, uterus and prostate, for leukaemia and for all cancers for the EU-28 in the period 1970–2009, and up to the most recent available year for six European countries (France: 2009; Germany: 2011; Italy: 2010; Poland: 2011; Spain: 2011; UK: 2010). Age-standardised (world population) mortality rates from lung cancer in the EU-28 will continue to decline in males (fig. 3), with shallower declines in Spain and France, while Poland will maintain the highest rate. In contrast, the steady increase in age-standardised mortality in females in the EU-28 is expected to continue (fig. 3). The different trends of male and female mortality rates suggest against the possibility that the reduced mortality observed in males depends on improved treatment of lung cancer but rather reflect

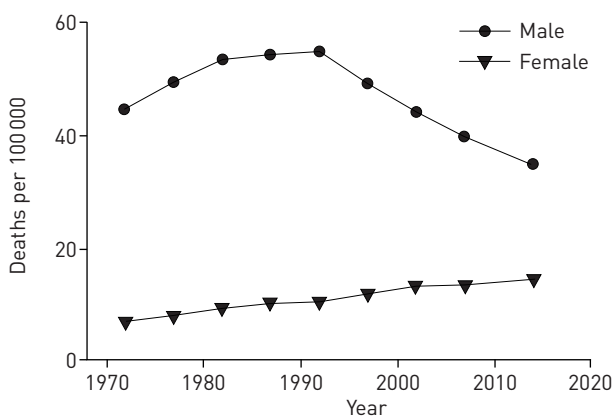

Figure 3. Trends of age-standardised (world population) lung cancer mortality throughout quinquennia from 1970–1974 to 2005–2009 and predicted rates for 2014, for males and females in the 28 member states of the European Union. Reproduced and modified from [15] with permission from the publisher.

Table 2. Lung cancer risk factors

- Tobacco smoking, second-hand smoke
- Chromium
- Silica
- Coal smoke and indoor emission from other fuels
- Radiotherapy for lymphoma and breast cancer
- Diesel exhaust COPD
- Pulmonary fibrosis
- Asbestos
- Beryllium
- Air pollution
- Genetic predisposition
- TB scarring
- Radon and its decay products
- Arsenic

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the decrease in male incidence due to the change of smoking habit that has occurred in males but not in females in the second half of the 20th century. This is further confirmed by the constant overall mortality to incidence ratio of lung cancer throughout recent years. If this trend continues, by 2015, lung cancer is expected to become the first cause of cancer mortality in females.

Smoking and other r2isk factors

The principal risk factors for lung cancer are shown in table 2. As the gap in tobacco consumption between males and females decreases, so will the sex differences in rates of lung cancer.

Most lung cancers are caused by cigarette smoking, with a strong relationship to dose and duration of exposure [16, 17]. In addition, approximately 10–20% occur in lifelong nonsmokers, causing some 150 000–250 000 deaths per year worldwide [18]. Nonsmokers who are exposed to second-hand smoke at home or in the workplace increase their lung cancer risk by 20–30%. Second-hand smoke exposure caused more than 7300 lung cancer deaths annually for 2005–2009 among adult nonsmokers in the USA [19]. The exposure to second-hand smoke has substantially decreased in recent years, as a consequence of a growing number of laws that prohibit smoking in workplaces and public places, including restaurants and bars. In addition, the increase in the number of households adopting voluntary smoke-free home rules may further contribute to limiting the exposure to passive smoking [19].

Exposure to a number of chemical agents and substances, either in the workplace or in the general environment, has been associated with lung cancer [18, 20]. It was first in the 1920s–1930s that investigators proposed radiation or radon gas exposure as a putative aetiological agent [20]. Later, the decay products of radon rather than radon itself were thought to be the prominent "mutagenic" factors to bronchial cells [21]. This topic and other risk factors of lung cancer are dealt with in detail in other chapters of this *Monograph*.

Screening for lung cancer

It is known that, at the age of 65 years, 8.9% of male current smokers will die of lung cancer in the subsequent 10 years *versus* 0.4% of never-smokers. For females, the corresponding figures are 5.5% *versus* 0.5%. Furthermore, minimally invasive surgical techniques have greatly improved the diagnosis and treatment of lung cancer in industrialised countries. This suggests that screening programmes for the early detection of lung cancer in populations at

risk might help to reduce mortality rates for the disease. In contrast with other cancer types, however, lung cancer has lacked an effective screening tool, and this has been the subject of considerable controversy [22].

Some promising progress on this controversial topic stems from the results of a recent study showing that low-dose computed tomography (LDCT) scanning in current or former cigarette smokers achieved positive screening results more than three times higher than radiography. In addition, the number of lung cancers detected by LDCT screening was increased by a factor of 2.7, and lung cancer-specific mortality was decreased by roughly 20% [23]. These results confirm and further extend those of previous studies [24, 25], thus contributing to the incorporation of LDCT screening in the guidelines issued by the American Association for Thoracic Surgery [26].

It should be considered, however, that the benefits of screening for lung cancer using LDCT are somewhat reduced by the occurrence of false-positive results in 22.3% more people than when using radiography (36.5% *versus* 14.2%), and by the unnecessary use of invasive procedures in 1.8% more people with false-positive LDCT (2.5% *versus* 0.7%) [23].

Pleural mesothelioma

Malignant pleural mesothelioma is a highly lethal and aggressive tumour with an overall poor prognosis. It derives from multipotent mesothelial cells, which differentiate into malignant elements. The mechanisms determining this differentiation as well as the local invasiveness of mesothelioma are poorly understood, and relatively few efforts have been made to understand the mechanisms underlying the pathogenesis of this tumour. After the occurrence of mesothelioma was first reported in 1960 in workers exposed to blue asbestos (crocidolite) [27], a huge number of experimental and epidemiological studies published up to the present has proved causality between asbestos mineral fibres and mesothelioma [28–33]. In the last two decades, geographic clusters of mesothelioma have been reported in populations with non-occupational environmental exposure to asbestos or other mineral fibres, including erionite [34], a fibrous zeolite found in the village of Karain (Turkey), and fluoro-edenite [35–37], a new amphibole end-member of volcanic origin found in Biancavilla, a small town in the eastern region of Mount Etna (Sicily), which is chemically different from known asbestos types. In both cases the local populations are exposed because of inadvertent use of both these minerals for building and road construction. The occurrence of "para-occupational" mesothelioma among family members of workers who bring home their contaminated work wear has also been reported [38, 39]. Despite growing interest, the epidemiology of mesothelioma is rather neglected in cancer statistics and reports, so little information is available as yet. In Europe, national mesothelioma registers are accessible for some countries, including the UK, Scandinavia, Belgium and Italy.

Incidence and mortality

There is uncertainty about the global burden of mesothelioma. It has been estimated that as many as 43 000 people worldwide die from all forms of mesothelioma each year [40]. The 5-year survival of people with mesothelioma is roughly 8%. Consequently, the mortality to incidence ratio is high and the mortality rate of malignant mesothelioma may be used as a surrogate of new-case incidence. Estimated deaths from pleural mesothelioma are 41% and those from mesothelioma of unspecified sites (including the unknown pleural cases) are 43% of all mesothelioma deaths. These outnumber deaths from mesothelioma of the peritoneum

and pericardium, which account for 4.5% and 0.3%, respectively [41]. The pleura is the most frequent primary site of mesothelioma, with pleura to peritoneum ratios of 13:1 in Australia; 8:1 in Japan and 7.3:1 in Sweden.

Given the strong specific association between asbestos and mesothelioma, the patterns of incidence and mortality of this tumour should reflect those of occupational exposure to asbestos. For this reason, the current incidence of malignant mesothelioma is higher among males than females, particularly in the male workforce [33, 41]. For example, according to the French National Mesothelioma Surveillance Program, the risk fraction attributable to occupational asbestos exposure is more than 80% in males and less than 40% in females [32]. This difference in risk fraction attributable to asbestos exposure in the workplace has also been reported elsewhere [33, 40]. The annual crude incidence rates of pleural mesothelioma in different European countries are estimated at around 30 cases per million in Belgium and the UK, and 21 cases per million in the Netherlands, while other European countries such as Germany, Italy, Denmark and Norway have crude incidence rates between 11 and 20 cases per million. Incidence rates below 11 cases per million are reported or estimated in the Iberian peninsula and Ireland [31, 42].

PETO *et al.* [30] designed a model of pleural cancer mortality from 1970 to 1989 for six European countries (UK, France, Germany, Italy, the Netherlands and Switzerland). The ratio of mesothelioma to recorded pleural cancer mortality was 1.6:1 in the UK, and assumed to be 1:1 in other countries. Projections for the period 1995–2029 suggest that the number of males dying from mesothelioma in western Europe each year will almost double over 20 years, from 5000 in 1998 to about 9000 around 2018, and then decline, with a total of about a quarter of a million deaths over the next 35 years [30]. In Spain, deaths from mesothelioma are expected to continue to increase until at least 2016, as the use of asbestos was banned in 2001 [43].

Pleural mesothelioma, which is most commonly diagnosed at 50–70 years of age, is also responsible for the highest fractions of mortality and DALY in the same age group [40]. Age-standardised mortality rates vary considerably between European countries (table 3) and there is a strong correlation between mesothelioma mortality rates and the amount of asbestos imported by each country, but in most there has been a steady increase during the last few decades. A recent study reports that world mesothelioma deaths will peak in the 2030s and thereafter decline. It has also been seen that the annual number of mesothelioma deaths in the UK has risen increasingly rapidly, from 153 deaths in 1968 to 1848 in 2001, and is predicted to peak at around 1950–2450 deaths per year between 2011 and 2015. Following this peak, the number of deaths is expected to decline rapidly [44]. However, peak periods of mesothelioma deaths in developing countries and countries where the bulk of asbestos is used today are expected by the 2050s [44].

Despite clear-cut evidence that the main cause of malignant mesothelioma is exposure to asbestos and other mineral fibres [34, 36], there seems to be a spontaneous "basal" incidence of the tumour, which has been estimated to be approximately one case per million per year [29], occurring even in children [45]. It must be taken into account, however, that some of the spontaneous mesothelioma might be due to unrecognised exposure; if so, the basal incidence of mesothelioma would be lower than one per million.

Risk factors

Given the widespread occupational use and environmental distribution of asbestos and asbestos-like fibres, individuals can be exposed in many different situations and

Table 3. Mortality rates for mesothelioma

Age-standardised rate per 100 000	Countries
⩾1.0	Belgium, the Netherlands, Iceland, Norway, Denmark, France, Germany, Italy, UK, Croatia, Slovenia
0.5–0.9	Spain, Austria, Sweden, Finland, Ireland
0.1–0.4	Estonia, Latvia, Lithuania, Poland, Czech Republic, Slovakia, Hungary, Romania, Serbia, Portugal
<0.1	Montenegro, Bulgaria, Republic of Moldova
No data	Switzerland, Bosnia Herzegovina, Albania, Macedonia, Greece, Turkey, Russia

Data from [42].

circumstances during their lifespan. The development of mesothelioma after asbestos exposure involves individual susceptibility, but the genetic determinants of the disease are poorly understood. According to current evidence, multiple types of chromosomal abnormalities may be involved and malignant mesothelioma cells harbour multiple key genetic mutations, which mainly inactivate tumour suppressor genes [46, 47]. Mesothelioma has long been considered a representative type of tumour primarily caused by environmental factors, especially asbestos, but familial cases of mesothelioma with a specific gene mutation have challenged this idea. The existence of a genetic basis is further supported by family aggregation of mesothelioma cases, although it can be argued that aggregation might also be explained by living in the same environment with common exposure to asbestos. Therefore, it may be difficult to separate inherited predisposition from environment. It is likely, however, that as for many other neoplastic diseases, mesothelioma is the result of a combination of genetic and environmental causes.

The term ‘‘asbestos’’ is used to collectively indicate a number of different naturally occurring minerals. Chrysotile, the serpentine form of asbestos, which accounts for 80–90% of commercially used asbestos, seems to have a low potential for causing mesothelioma. In contrast, the amphibole varieties amosite, crocidolite, tremolite and anthophyllite are considered substances with the highest tumour-causing potential. European countries have an irregular regional distribution of mesothelioma because of variable activities of asbestos extraction and manufacturing. The areas of the world that have the highest incidence of malignant pleural mesothelioma are those with asbestos mines, as well as industrialised countries that use large amounts of asbestos for shipyards, construction and insulation. Despite the synergistic effect of smoking and asbestos in the occurrence of lung cancer, there is no evidence that tobacco smoking increases the risk of malignant mesothelioma [33].

Two other important factors have been considered in interpreting the relationship between asbestos and mesothelioma: the latency period and the dose characteristics of exposure. The latency period, *i.e.* the time interval between the first exposure to asbestos and tumour appearance, is on average 30–45 years or even longer. Discrepancies among the values of the latency period in various case series may be explained by the duration and intensity of asbestos exposure or by differences in genetic susceptibility. The dose–response relationship confers a long-term risk of developing malignant pleural and peritoneal mesothelioma that increases following cessation of exposure. Whereas the rate of increase appears to start to level out after 40–50 years, no one survives long enough for the excess risk to disappear [48].

In addition, people differ in their susceptibility to development of mesothelioma after similar levels of asbestos exposure, possibly due to the differences in genetic polymorphisms or expression levels of genes involved in the DNA repair system and epigenetic modification.

Furthermore, some occupational groups have only recently been recognised as categories at risk for mesothelioma. For example, an increased risk of mesothelioma was observed among 16 422 male firefighters in five Nordic countries [49].

Conclusion

The scientific evidence that stems from epidemiological studies is fundamental for primary and secondary disease prevention. Epidemiology studies on lung cancer help to assess disease occurrence, to characterise its natural history and to identify disease determinants. These and other aspects of epidemiological approaches may be of pivotal value for designing intervention programmes, either based on risk factor prevention or population screening and gene susceptibility recognition, as well as for shaping preventive measures and resource allocation.

For lung cancer, case–control cohort studies and large population surveys have allowed not only the establishment of the causative relationship with cigarette smoking but also the identification of other risk factors, some of which act in concert with smoking to increase the risk synergistically. These factors include radon and its decay products, asbestos, arsenic, nickel, beryllium, chrome derivatives, aromatic hydrocarbons, chloromethyl ethers, diesel exhaust, smoke from coal and other fuel combustion, and other mutagenic agents.

The 1-year relative survival for lung cancer increased up to 40% in the last 10 years, largely due to improvements in minimally invasive surgical techniques and combined therapies. The 5-year survival rate for all stages combined is only 15%. In contrast, the 5-year survival rate is 50% or higher for cases detected when the disease is still localised, thus suggesting the potential benefits of screening programmes for early diagnosis in high-risk people. Despite some promising results of recent research, however, there have been only slight improvements in early diagnosis and survival, reflecting limited advances in screening and treatment for lung cancer. The identification of host differences in susceptibility to lung carcinogens, in particular to cigarette smoke, is essential in predicting who is at highest risk. Susceptibility differences in the form of rare, high-penetrance genes are suggested from studies of familial aggregation of lung cancer and a linkage study.

Lung cancer is commonly considered a "preventable" disease. However, so far, its heavy worldwide burden substantiates the relative weakness and inefficacy of preventive measures, including the reduction of smoking as well as the conduction of screening programmes and early detection of lung cancer.

Malignant mesothelioma is an aggressive tumour arising primarily from the pleural or peritoneal cavities, which develops due to asbestos exposure after a long latency and is highly refractory to conventional therapeutic modalities. Molecular genetic analysis has revealed several key alterations of onco-suppressor genes, which are responsible for the development and progression of malignant mesothelioma. However, frequent activating mutations of any oncogenes have not been clearly identified yet, which is one of the reasons that current molecular target therapy is not very effective for mesothelioma patients. Recent studies have also found characteristic epigenetic alterations in mesothelioma, which include distinct DNA

methylation patterns and the involvement of noncoding ribonucleic acid. With further comprehensive genome analyses, new genetic and epigenetic alterations in mesothelioma cells are expected to be revealed more precisely. Hopefully, knowledge of these new aspects would be applied in the development of new diagnostic tools and novel target therapies against malignant mesothelioma. Further epidemiological studies are of paramount importance to identify the European regions where asbestos is still present and to monitor exposed populations as well as to conduct programmes for the efficient removal of asbestos contaminating the environment.

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Pneumonia and other infectious diseases

Francesco Blasi[1], Paolo Tarsia[1] and Tobias Welte[2]

This chapter describes the epidemiology of CAP and influenza in Europe. CAP is still a substantial cause of hospitalisations and death across Europe. Hospitalisation rates differ widely across Europe. Aetiological studies across the continent consistently report *Streptococcus pneumoniae* as the leading pathogen, irrespective of the site of patient management. Costs associated with pneumonia are largely associated with hospitalisation, with diagnostics and antibiotic treatment covering a marginal quota of expenses. In addition to direct mortality, patients with pneumonia are more prone to long-term mortality compared with matched populations.

Seasonal epidemics of influenza typically spread through Europe during the winter months carrying a considerable socioeconomic burden. Influenza pandemics occur at 10–40-year intervals. The last pandemic, caused by an H1N1 virus, was of moderate intensity and was associated with excess deaths primarily among children, often without underlying diseases.

Data on influenza vaccination coverage in Europe indicate that, on average, coverage levels are below those set by World Health Organization and European Union standards.

Although the past decades have shown a decreased impact of infections in industrialised countries, LRTIs are still a cause of substantial morbidity and mortality worldwide. Data from the World Health Organization (WHO) show that between 1990 and 2010 there was a 17.6% reduction in mortality caused by LRTIs, a 14.6% reduction in influenza-associated deaths and a 3.6% reduction in pneumococcal pneumonia-related mortality globally [1]. Among subjects aged 15–49 years, LRTIs were responsible for 3.2% of female deaths and 2.8% of male deaths worldwide in 2010, and 2.3% of mortality in the WHO European Region in 2008. LRTIs ranked as the third leading cause of death globally in 1990, and as fourth cause in 2010. Regional breakdowns showed that LRTIs were the eighth leading cause of years of life lost in central Europe, and the ninth cause in both eastern and western Europe [1]. It is projected that the percentage of deaths worldwide attributable to LRTIs will be 5.5% in 2015 and 4.2% in 2030.

DALYs have been used as an absolute measure of disease-related health loss. DALYs are calculated as the sum of years of life lost due to premature mortality and the years lived with disability attributable to a specific disease. Between 1990 and 2010, there was a 44.2% drop in

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DALYs attributable to LRTIs, a 40.7% drop in DALYs attributable to influenza and a 38% drop in pneumococcal pneumonia-associated DALYs worldwide [2]. LRTIs ranked first as the global cause for DALYs lost in 1990 and were estimated to rank second in 2010. Regional breakdown of the data shows that LRTIs were the 13th cause of DALYs lost in eastern Europe, the 17th cause of DALYs lost in central Europe and the 21st cause of DALYs lost in western Europe [2]. In the WHO European Region, LRTIs are associated with 1.5% of lost DALYs. It is projected that LRTIs will be responsible for 4.6% of total DALYs lost worldwide in 2015 and 3.2% in 2030.

Community-acquired pneumonia

Incidence

Studies on the incidence of CAP have been carried out in a number of European countries [3–19]. Table 1 lists European studies reporting pneumonia incidence rates. The overall annual incidence of CAP in adults ranges between roughly 1.7 cases per 1000 people in southern countries such as Italy and Spain, to 11.6 cases per 1000 people in Finland. In the European Union (EU), this translates into an annual number of expected pneumonia cases of approximately 3 370 000 [21]. Pneumonia incidence appears to increase with age, male sex, the presence of comorbidity and during the winter months. There appears to be a higher incidence in northern European countries compared with southern Europe, although differences in study populations and measures used for incidence rates make it difficult to make direct comparisons across studies. In most cases, studies have analysed CAP incidence in relatively restricted areas of individual countries, over different periods in time, and may not be fully representative of the nation as a whole. Notable exceptions include, for example, the German mandatory documentation of all hospital inpatients with CAP in 2005 and 2006 [6].

Risk factors

Significant risk factors that increase CAP incidence have been identified. These include demographic factors, such as age and male sex (as previously mentioned), and residing in a nursing home. A number of risk factors may be attributable to lifestyle conditions such as alcohol use, smoking and poor oral hygiene [22, 23].

Chronic respiratory conditions increase the likelihood of CAP. In particular, patients with COPD may constitute up to a third of the population of CAP patients in hospitalised cohorts [24]. Chronic cardiovascular diseases, cerebrovascular disease/stroke and dementia, together with chronic renal or liver disease and diabetes mellitus, are all recognised as factors that increase the rate of pneumonia in adults between two- and four-fold [22, 23, 25].

In addition, immunosuppressive conditions, both due to medication use or induced by clinical diseases such as asplenia, primary immunodeficiencies and HIV infection, are associated with several-fold higher risks of CAP [22, 23, 25]. The main risk factors for CAP are summarised in table 2.

Hospitalisation rate

The percentage of CAP patients who are admitted to hospital varies considerably across European countries, with figures ranging between 20% and 41.5% in different studies. This

Table 1. Incidence of CAP in different European countries

Country	First author [ref.]	Study period	Age years	Pneumonia incidence	Reporting
Finland	Jokinen [3]	1981–1982	All ages	11.6 (13.9 M, 9.4 F)	Cases per 1000 population
			15–29	4.2 M, 4.6 F	
			30–44	5.6 M, 5.9 F	
			45–59	9.8 M, 7.0 F	
			60–74	25.0 M, 9.0 F	
	Palmu [4]		>75	65.2 M, 19.6 F	Cases per 1000 person-years
			>65	5.5	
Germany	Schnoor [5]	2003	>18	8.7	Cases per 1000 population
	Ewig [6]	2005–2006	All ages	3.21 M, 2.52 F	Cases per 1000 person-years
			20–29	0.44	
			30–39	0.63	
			40–49	0.77	
			50–59	1.34	
			60–69	2.98	
			70–79	7.39	
			80–89	17.62	
			>90	35.81	
Italy	Rossi [7]	1997–1999	All ages	1.6	Cases per 1000 population
			<65	0.8	
			>65	4.8	
	Viegi [8]	1999–2000	All ages	1.7 M, 1.7 F	Cases per 1000 population
			15–44	0.9	
			45–64	1.6	
			>64	3.3	
Portugal	Froes [9]	1998–2000	>15	2.7	Cases per 1000 population
			>65	9.8	
Spain	Almirall [10]	1993–1995	All ages	1.6	Cases per 1000 population
			15–39	1.2 M, 1.0 F	
			40–64	1.8 M, 1.4 F	
			>64	5.2 M, 1.9 F	
	Monge [11]	1995–1996	All ages	1.6	Cases per 1000 population
			>65	5.2	
	Gutiérrez [12]	1999–2001	Outpatients		Cases per 1000 population
			All ages	1.6 M, 0.9 F	
			15–44	0.8 M, 0.6 F	
			45–64	1.4 M, 0.7 F	
			65–74	3.2 M, 1.6 F	
			>75	8.7 M, 3.0 F	
			Inpatients		
			All ages	0.9	
	Ochoa-Gondar [13]	2002–2005	Outpatients		Cases per 1000 person-years
			All ages	4.2 M, 2.9 F	
			65–74	3.0 M, 2.2 F	
			75–84	5.3 M, 2.8 F	
			>85	10.0 M, 7.9 F	
			Inpatients		
			All ages	15.1 M, 7.0 F	
			65–74	11.1 M, 4.3 F	
			75–84	19.9 M, 8.71 F	
			>85	29.0 M, 16.4 F	

Table 1. Continued

Country	First author [ref.]	Study period	Age years	Pneumonia incidence	Reporting
	Vila-Corcoles [14]	2002–2005	Oupatients	3.5	Cases per 1000 person-years
			>65		
			Inpatients	10.5	
			>65	3.0	
	Sicras-Mainar [15]	2008–2009	All ages	1.8	Cases per 1000 population
			18–49	3.2	
			50–64	5.2	
			65–74	8.1	
			>75		
Sweden	Hedlund [16]	1987–1988	18–49	19	Cases per 1000 person-years
			50–64	69	
			65–84	120	
			>85	242	
UK	Melegaro [17]	1995–2000	15–44	0.2	Cases per 1000 population
			45–64	0.5	
			65–74	1.5	
			>75	4.0	
	Trotter [18]	1997–2005	<65	0.65–0.84	Cases per 1000 population
			65–74	2.63–3.55	
			75–84	6.8–8.8	
			>85	16–22.4	
Czech Republic	Tichopad [19]	2009	5–64	1.93	Cases per 1000 person-years
			65–74	4.18	
			75–84	10.99	
			85–99	22.51	
Slovakia	Tichopad [19]	2009	5–64	2.48	Cases per 1000 person-years
			65–74	5.71	
			75–84	12.33	
			85–99	19.31	
Poland	Tichopad [19]	2009	5–64	1.48	Cases per 1000 person-years
			65–74	4.00	
			75–84	8.72	
			85–99	16.75	
Hungary	Tichopad [19]	2009	5–64	4.08	Cases per 1000 person-years
			65–74	8.82	
			75–84	17.77	
			85–99	52.03	

M: male; F: female. Data from [3–19]. Reproduced and modified from [20] with permission from the publisher.

translates into roughly 1 000 000 hospital admissions for CAP per year in the EU, accounting for 2% of total hospitalisations in EU countries. Differences in hospitalisation rates are probably due to heterogeneous admission criteria, differing healthcare systems and the period of the year during which the study was conducted. Hospital admissions depend on age and the highest rates may be observed in subjects aged over 65 years. Over the past decade, studies conducted both in northern Europe (Denmark, the Netherlands and the UK) [18, 26, 27] and in southern Europe (Portugal) [28], have indicated an increase in hospitalisation rates for pneumonia of the order of 30%.

In a Spanish series, 8–10% of patients admitted to the hospital for CAP required ICU care [10]. In a German nationwide study of hospitalised CAP, 16.5% of patients were in CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or

Table 2. Identified risk factors for CAP

Immunocompetent at risk	Immunocompromised at risk
Demographics	**Immunosuppression**
Age >65 years	Autoimmune disease receiving steroids or immunosuppressive therapy
Male sex	Cancer patients receiving immunosuppressive therapy
Nursing home	**Immunocompromised**
Lifestyle	Asplenia/splenic dysfunction
Alcoholism	Primary immunodeficiencies
Smoking	HIV infection
Poor oral hygiene	
Underlying diseases	
Chronic heart disease	
Chronic renal disease	
Chronic liver disease	
Chronic respiratory disease	
Diabetes mellitus	

⩽60 mmHg (diastolic), age ⩾65 years) risk class 1, 71.55% in risk class 2 and 11.91% in risk class 3 [6]. Approximately 6% received ventilatory support at admission or during their hospital stay.

Aetiology

Identification of the microbiological agent responsible for CAP is often elusive. Even in epidemiological studies, using extensive and costly diagnostic procedures, an aetiological agent is only found in up to 60% of cases with CAP (table 3) [29]. Conversely, in everyday daily clinical practice, a microbiological diagnosis is reached in only 20% of cases. Therefore, in most experiences, the largest aetiological group is that with "no microbiological finding".

Table 3. Aetiology of CAP in Europe based on treatment setting

Pathogen	Mean %		
	Outpatient	Hospital	ICU
Streptococcus pneumoniae	38	27	28
Mycoplasma pneumoniae	8	5	2
Haemophilus influenzae	13	6	7
Chlamydophila pneumoniae	21	11	4
Staphylococcus aureus	1.5	3	9
Enterobacteriaceae	0	4	9
Pseudomonas aeruginosa	1	3	4
***Legionella* spp.**	0	5	12
Coxiella burnetii	1	4	7
Respiratory viruses	17	12	3
Unknown	50	41	45

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The results of epidemiological studies must be placed into context according to site of treatment (at home or in the hospital), patient characteristics (age, sex and comorbidities), season of the year considered and reliance on newer diagnostic techniques (antigen test and molecular biology techniques). Although it is still debated whether the use of more extensive diagnostic techniques is associated with better diagnostic yield, it is estimated that implementation of pneumococcal urinary antigen testing alone may identify an additional 11% of cases of pneumococcal pneumonia compared with reliance solely on blood culture and sputum examination [30]. Factors associated with unknown aetiology in hospitalised CAP patients include age >70 years, presence of kidney or cardiac comorbidities, or nonalveolar radiological infiltrates [31].

In a recent review of 46 European articles on the aetiology of pneumonia, *Streptococcus pneumoniae* emerged as the leading single pathogen in all countries [20]. Identification rates varied between 11.9% in Italy and 68.3% in Finland (mean: 35% of cases). Other commonly reported pathogens include: *Haemophilus influenzae* (between 2.4% in Estonia and 14.6% in Switzerland), *Legionella* spp. (between 0% in Estonia, Finland and Ireland, and 12.9% in Spain), *Staphylococcus* spp. (0% in Finland, Ireland and Slovenia, to 11.7% in France), *Moraxella catarrhalis* (0% in Germany to 12% in Estonia), *Mycoplasma pneumoniae* (0.7% in France to 32.4% in Slovenia), *Chlamydia* spp (0% in Ireland to 26.5% in Slovenia), and viruses in up to 16.5% of cases. No pathogen was identified in between 35.3% and 67.3% of cases [20].

In a recent meta-analysis of 24 423 CAP episodes in 77 epidemiological studies conducted in Europe between 1985 and 2008, 4714 (19.3%) cases were attributable to *S. pneumoniae* [32]. By using a mixed-effects meta-regression model, it was found that, compared with CAP cases treated at home, the odds of *S. pneumoniae* being the cause of CAP was 1.45 (95% CI 1.19–1.77) times higher for hospitalised cases and 2.33 (95% CI 1.80–3.02) times higher for patients admitted to the ICU. Furthermore, the study found that the odds of detecting *S. pneumoniae* as a cause of CAP in studies from western and southern Europe were two and three times smaller, respectively, compared with studies conducted in northern Europe [32].

The primary role of *S. pneumoniae* as a pathogen in CAP has been confirmed, irrespective of whether the patient is managed at home, in a hospital ward or in an ICU (table 2). Most of these studies have been carried out in the hospital setting. In defining the aetiology of CAP among subjects treated as outpatients, it must be kept in mind that some studies in the literature focus on true primary care cases that are referred to primary care physicians, while others consider patients referred to the emergency department and managed at home. In addition, some studies are based on patients with "lower respiratory tract infections", and do not require a chest radiograph to confirm the presence of pneumonia, whereas in other studies a chest radiograph is mandatory.

In a recent prospective observational study carried out in Barcelona, Spain, on 586 consecutive outpatients with CAP, an aetiological diagnosis was established in 188 (33.1%) patients [33]. The most frequent pathogens were *S. pneumoniae* (n=66; 35.1%), followed by *M. pneumoniae* (n=29; 15.4%), respiratory viruses (n=25; 13.3%), *Legionella pneumophila* (n=13; 6.9%), *Coxiella burnetii* (n=11; 5.9%), *Chlamydophila pneumoniae* (n=10; 5.3%) and *H. influenzae* (n=9; 4.8%). More than one causative agent was found in 17 (9.0%) of patients, with *S. pneumoniae* being the most frequently involved agent in mixed infections (82.4%). Complications were rare (5.3% of patients, mostly pleural effusion and empyema), only 2.3% required hospital admittance (70% of whom had comorbidities) and mortality was low (0.5%).

In a study specifically investigating CAP in younger patients (aged <65 years) conducted in Germany, *S. pneumoniae* was the leading pathogen, identified in 9.2% of patients, closely followed by *M. pneumoniae* (8.4% of patients) [34]. In particular, *M. pneumoniae* was the leading pathogen among younger outpatients and those with no comorbidities. Patients aged <65 years were free of comorbidity in over 50% of cases, mostly presented with mild CAP (74% with a CURB-65 (confusion, urea >7 $mmol \cdot L^{-1}$, respiratory rate ⩾30 $breaths \cdot min^{-1}$, blood pressure <90 mmHg (systolic) ⩽60 mmHg (diastolic), age ⩾65 years) score of 0) and showed very low short-term mortality (1.7%).

European studies investigating the aetiology of nursing-home pneumonia have also identified *S. pneumoniae* as the principal pathogen. EWIG *et al.* [35] investigated patients with nursing-home acquired pneumonia within the CAPNETZ (German Competence Network for Community-Acquired Pneumonia) database in Germany. *S. pneumoniae* was identified in 7.3% of the total population and in 9.1% of those with microbiological sampling. Enterobacteriaceae ranked second (3.3% in the total population, 4.5% in those with microbiological sampling), followed by *Legionella* spp. (2.5% in the total population, 3.6% in cases with microbiological sampling) and *Staphylococcus aureus* (2.3% in the total population, 3.1% in cases with microbiological sampling). *M. pneumoniae* was virtually absent (0.2% in the total population, 0.3% in cases with microbiological diagnosis). In a similar study conducted in Spain among nursing home residents with either probable or definitive aetiology of a pneumonia episode, *S. pneumoniae* was identified in 22% of cases, Enterobacteriaceae in 4%, *L. pneumophila* in 2%, and *S. aureus* in 2% [36].

Healthcare costs

The overall cost of pneumonia to health systems in Europe in 2011 was set at €2.5 billion for direct costs (primary care, hospital inpatient and outpatient care, drugs and oxygen). In addition, pneumonia accounted for 790 000 DALYs lost per year, with an annual monetised value of €43.5 billion, thus reaching a total annual cost of €46.0 billion [37].

Estimates of direct and indirect costs of treating CAP have been made in different European countries. A retrospective analysis of hospital discharge data from the Spanish national surveillance system conducted between 1995 and 1996 found that each year pneumonia was responsible for approximately 842 and 6347 days of hospitalisation per 100 000, in persons <65 and >65 years of age, respectively [11]. This equated to a cost of €114.8 million for the Spanish National Health Care System. Care of patients aged >65 years accounted for €66.8 million. An Italian study performed between 1999 and 2000 estimated that the yearly costs for treating a patient with CAP, including healthcare costs during the follow-up period, were €1586.90 [38]. A population-based study in Spain conducted between 1993 and 1995 estimated that the mean direct cost for treatment of CAP was €1553 in patients that required hospitalisation, which was 7.9 times higher than the €196 costs in subjects managed as outpatients [39]. Interestingly, 15.7% of admissions were considered inappropriate, and the length of hospital stay could have been reduced by 3.5 days in some cases. It was estimated that a reduction in inappropriate admissions and undue length of stay would have resulted in a 17.4% cost containment. In a prospective study conducted on 580 CAP patients in 22 German hospitals in 2003, the median cost of treatment for a hospitalised patient was $1333 [40]. Median costs for patients admitted to the ICU were $2300, compared with $1242 in non-ICU patients. Costs for personnel and accommodation were major contributors to total direct costs, with costs for diagnostics and antibiotic therapy accounting for only 7.6% of total costs.

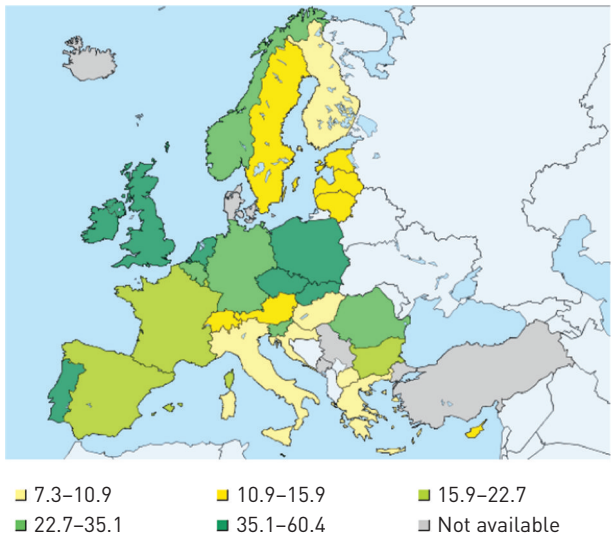

Figure 1. Death due to pneumonia by sex in 2010. Data are presented as standardised death rate per 100 000 inhabitants. As most causes of death vary significantly with people's age and sex, the use of standardised death rates improves comparability over time and between countries, as they aim at measuring death rates independently of different age structures of populations. The standardised death rates used here are calculated on the basis of a standard European population (defined by the World Health Organization). Reproduced and modified from [41] with permission and modified from the publisher.

In a retrospective analysis of CAP administrative data conducted in eastern European countries in 2009, the total healthcare costs attributable to the disease were €12 579 543 in the Czech Republic, €9 160 774 in Slovakia, €22 409 085 in Poland and €18 298 449 in Hungary [19]. Hospitalisation represented >90% of direct costs. The burden of CAP increased with age, with hospitalisations driving the costs of CAP upwards in the elderly population.

Mortality

Mortality caused by CAP in Europe is still considerable. In 27 EU countries in 2010, pneumonia caused 10 deaths per 100 000 inhabitants among females and 17 deaths per

Table 4. Risk factors associated with CAP mortality

Age >65 years
Male sex
Use of corticosteroids
Hospital-acquired lower respiratory tract superinfection
Polymicrobial pneumonia
Pleural effusion
ICU admission
Recent hospitalisation
Serious underlying disease
Acute renal failure
Bacteraemic pneumonia
Ineffective initial treatment
Multilobar involvement
Impaired alertness
Septic shock

100 000 inhabitants among males, and was responsible for 3.5% of total deaths (fig. 1) [41]. A review of CAP studies conducted in Europe reported extremely variable mortality rates, ranging from 1% to 48% [20]. This variability depends on multiple factors including demographics, comorbid conditions and ambulatory *versus* hospital setting for treatment. The risk factors associated with CAP mortality are listed in table 4.

CAP mortality among patients diagnosed in the emergency department but treated at home may be as low as 0.5% in the Barcelona area [33]. German data from the CAPNETZ database shows 0.8% mortality among outpatients and 12.2% among hospitalised patients [42]. In a previously quoted mandatory German report on CAP, overall in-hospital mortality was 13.72% in 2005 and 14.4% in 2006 [6]. Most deaths occurred within the first days after hospitalisation. CAP in-hospital mortality in eastern European countries (Czech Republic, Slovakia, Poland and Hungary) appears to be greater (19.1%), ranging 18–22% among patients aged >50 years and 21–25% among those aged >65 years [19]. One study employed data from centres participating in the CAPO (Community-Acquired Pneumonia Organization) International registry to evaluate mortality differences among different world regions [43]. In-hospital CAP mortality was highest in Latin America (13.3%), followed by Europe (9.1%) and North America (7.3%).

A very recent epidemiological survey presented data from 1166 patients with CAP admitted to 102 ICUs across 17 European countries [44]. Of these patients, 962 (84%) required mechanical ventilation within the first week of admission. ICU mortality was 19%, whereas overall in-hospital mortality was 24.4%. A multicentre French study investigated 282 severe pneumococcal pneumonia cases admitted to the ICU [45]. A total of 186 (84%) patients required mechanical ventilation. Hospital mortality reached 28.8%.

When considering the overall mortality burden of pneumonia, in addition to in-hospital mortality, long-term mortality must also be taken into account. A long-term follow-up Finnish study (median follow-up 9.2 years) found that elderly inpatient and outpatient CAP cases had significantly higher risks of death for several years, compared with elderly controls without pneumonia [46]. Pneumococcal aetiology was associated with an almost three-fold higher pneumonia-related risk. In a study conducted in general practice in the UK 3-year mortality in patients with CAP was 30.8% compared with 10.3% in controls [47]. In a Dutch cohort of CAP patients, long-term (7 years) mortality rates were more than three times as high as the general population [48].

Pneumococcal vaccination

Pneumococcal polysaccharide 23-valent vaccine (PPV 23) stimulates an immune response towards *S. pneumoniae* surface capsular antigens. Polysaccharides are T-cell-independent antigens that generally stimulate short-lived B-cell responses by driving the differentiation of B-cells into plasma cells to produce antibodies [49]. Thus, the protective effect is short-lived and is inconsistent 3–5 years following vaccination [50]. A Cochrane meta-analysis indicates that PPV23 is slightly effective in reducing invasive pneumococcal disease (IPD) in healthy adults [51]. The protective effect was absent in adults with chronic illness, a vulnerable population for pneumococcal disease. Likewise, the vaccine was not protective against pneumonia or all-cause mortality.

Conjugate vaccines induce both a B-cell-dependent and a T-cell-dependent response, and induce an anamnestic (memory) response to a booster dose of the vaccine [52]. The

heptavalent conjugate vaccine (PCV 7) introduced for childhood anti-pneumococcal immunisation significantly reduced the incidence of IPD in children with a noticeable herd effect on the incidence of IPD among non-vaccinated adults [53].

More recently, a 13-valent conjugate vaccine (PCV 13) has been marketed and approved for use in children and adults. Immunogenicity of PCV 13 appears to be superior and longer lasting than that of PPV 23 [54]. During the course of 2014, publication of the results of the large-scale CAPITA study on PCV 13 efficacy in adults conducted in the Netherlands should define the role of this vaccine in adult populations [55].

Influenza

Influenza is among the most common and important respiratory infections involving all age groups worldwide. Descriptions of the impact of influenza epidemics on human societies can be found in literature. It is presumed that the great plague described by Thucydides in the city of Athens in the year 430 BCE may have been due to an influenza virus pandemic [56]. In the Middle Ages, influenza infection was sometimes referred to as the "kind illness", due to its relatively mild clinical course compared with other more dreaded diseases such as smallpox [57]. During the 20th century, influenza pandemics occurred in 1918, 1957 and 1968, caused by influenza A viruses of the H1N1, H2N2 and H3N2 subtypes, respectively. In 2009, the most recent influenza pandemic arose from an influenza A H1N1 virus of swine origin. In addition to these worldwide pandemics, influenza viruses of various other subtypes, for example H5N1 and H7N7, are sporadically transmitted from animals to humans, often causing severe disease.

Human influenza viruses are single-stranded RNA viruses belonging to the Orthomyxoviridae family, which includes the genera influenza virus A, B, and C [58]. Only influenza A and B viruses cause epidemics in human beings, and are included in seasonal influenza vaccines. The main antigenic determinants of influenza A and B viruses are the haemagglutinin (H) and neuraminidase (N) transmembrane glycoproteins. Based on their antigenicity, influenza A viruses are further subdivided into 17 haemagglutinin (H1–H17) and 10 neuraminidase (N1–N10) subtypes [59]. Among the many subtypes of influenza A viruses, influenza A(H1N1) and A(H3N2) are currently circulating among humans.

The genetic makeup of the influenza virus allows frequent minor drifts every 2–5 years in response to selection pressure to evade human immunity (antigenic drift) [60]. Rarely, reassortment between human and nonhuman viruses results in larger shifts, in which a new virus subtype emerges and replaces the previously circulating one (antigenic shift). A new pandemic virus rapidly invades the human population with partial or no immunity and may cause severe illness worldwide [61].

Haemagglutinin plays a major role in viral binding to, fusion with and penetration of human tissue cells. Once inside tissue cells, influenza virus replication is very quick, with shedding of the first influenza viruses from infected cells occurring after only 6–12 h [62]. Infectivity of influenza virus particles depends on a number of factors including temperature, pH and salinity of the surrounding water, and ultraviolet irradiation. Under normal environmental conditions virus survival is short, whereas at 4°C, the half-life of infectivity is about 2–3 weeks in water [63]. Large numbers of replicating viruses are shed by infected persons into respiratory secretions. Coughing and sneezing disperses infected droplets into the air

contaminating and infecting close contacts. In addition, viral spread may occur through contaminated hands or surfaces, where influenza viruses may persist over time [64].

Seasonal influenza spreads easily throughout the population *via* outbreaks in schools, nursing homes, hospitals, *etc*. In temperate climates, seasonal epidemics occur mainly during winter (lasting for 1–2 months in each country, and across Europe for about 4 months), while in tropical regions, influenza may occur throughout the year, causing outbreaks less regularly. Globally, influenza occurs with an annual attack rate estimated at 5–10% in adults and 20–30% in children [65]. Although most cases recover quickly, epidemics can result in high levels of worker/school absenteeism and productivity losses. Hospital capacity may be overwhelmed during peak illness periods. In a typical year, the WHO estimates that the seasonal influenza epidemic causes 3–5 million cases of severe illness in humans and 250 000–500 000 deaths worldwide [1]. The number of deaths is proportional to the number of people infected, usually about 0.1%. In the EU between 40 000 and 220 000 deaths per year can be attributed to influenza infection, depending on the pathogenicity of the circulating viral strain [66]. Illness results in hospitalisation and death mainly among high-risk groups. These include children $<$2 years of age, adults aged $\geqslant$65 years, pregnant females, and people of any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood or metabolic diseases (such as diabetes), or weakened immune systems [67]. Post-influenza bacterial pneumonia is a major cause of morbidity and mortality among high-risk populations.

Pandemics

In addition to the previously quoted first supposed influenza pandemic reported in the literature in Athens [56], the first documented pandemic occurred in 1580, and since then, 31 influenza pandemics have been reported [68]. The six most recent pandemics occurred in 1889, 1990, 1918, 1957, 1968 and 2009. Thus, pandemics appear to have a certain periodicity that varies between 10 and 40 years. The interval has not significantly increased or decreased with the passage of time, suggesting that increases in world population and the expansion of air travel are not determining factors. Most pandemics develop in Asia and, from there, spread to the rest of the world. Pandemics are usually caused by a reassortant virus produced from existing strains that acquire one or more new genes, as happened during the 1957 and 1968 pandemics. By contrast, the 1918 pandemic was unique in that the entire virus was novel to humans [69]. Historical records suggest that pandemics may appear at any time of year and are not necessarily limited to the classical winter pattern of seasonal influenza epidemics. This is conceivably because the new genetic variant viruses spread differently in the absence of previous immunity in a highly susceptible human population.

It is estimated that during the 1918–1919 H1N1 influenza pandemic, roughly a third of the world population ($\sim$500 million people) was infected and had clinically apparent illness [70]. In Europe, this included two monarchs: King Alfonso XIII of Spain and King George V of England. Clinically, this was the most severe pandemic to date, with a case fatality rate of $>$2.5% compared with $<$0.1% in subsequent influenza pandemics. The total deaths worldwide have been estimated to be between 50 and 100 million [71]. Recent estimates using European data indicate that the 1918–1919 pandemic was associated with 2 640 000 excess deaths, equating to 1.1% of the total population in Europe [72]. Overall, the excess mortality was 3.5 times higher than that during the remaining part of the 1906–1922 period. The highest mortality peak occurred in all European countries between October and November 1918. The authors found a statistically significant negative correlation between excess mortality and latitude, with southern countries (Spain, Portugal and Italy)

experiencing significantly more deaths compared with northern countries (Finland and Norway) [72].

American estimates of excess deaths during the 1918–1919 pandemic indicate 400 000–675 000 (0.47–0.75% of the total population) [73]. These data are well below the European mortality data. It may be that at the end of World War I, exhausted healthcare systems, a frail population, and large army and civilian movements across the continent may have contributed to a greater influenza mortality impact in Europe.

Although the 1918–1919 H1N1 pandemic is known as the "Spanish flu", due to the first reports arising from the Spanish town of San Sebastian in February 1918 and the very high mortality toll in this country, it is fairly certain that the pandemic originated outside Europe, although where the virus first emerged is still debated [74].

During seasonal influenza epidemics, the mortality curve by age is typically U-shaped, with mortality peaks among the very young and the very old, and comparatively low rates at intermediate ages. By contrast, during the 1918 pandemic, a W-shape curve was observed with an additional peak in young adults 20–40 years of age. Overall, the 15–44 year-old age group was associated with 68.2% of all influenza-related deaths in Paris and 66.3% of deaths in Madrid [75]. The absolute risk of death was higher in those aged <65 years than in those aged >65 years. Persons <65 years of age accounted for 99% of deaths in 1918–1919. By comparison, subjects aged <65 years were associated with 36% of excess deaths in the 1957 H2N2 pandemic and 48% in the 1968 H3N2 pandemic [70].

In March 1957, an H2N2 strain emerged from the Yunnan province of China, replaced the circulating H1N1 virus and rapidly spread worldwide during the course of the next 6 months. What became known as the "Asian flu" killed 1–4 million people globally [76]. Approximately 15% of the population acquired the disease. The case fatality rate was 1 in 4000, with deaths mainly encountered among the very young and the very old [57]. In Europe, the pandemic spread particularly during October and November 1957. The incidence of influenza infection peaked in children (25–50% of cases) and was minimal in subjects aged >70 years (5–10%) [77, 78].

In 1968, in Hong Kong, an H3N2 strain replaced the circulating H2N2 strain, causing a pandemic that killed 1–2 million worldwide [79]. The pandemic showed two peaks, one during the 1968–1969 season and a second during the 1969–1970 season. In countries such as the UK and France, most deaths occurred during the second peak [80]. Rates of excess mortality for pneumonia and influenza in subjects <65 years of age grew 2.2–4.6-fold during the course of the pandemic [81].

The 2009 H1N1 pandemic virus was also known as the swine-origin influenza virus, as it was probably derived from viruses that had been circulating in pigs for years. However, there is no evidence that pigs played a role in its spread within human populations, as diffusion was primarily through human-to-human transmission [82]. Viral spread was first detected in Mexico in March 2009 [83], but cases rapidly spread to the USA and to the rest of the world, so that on June 11, 2009, the WHO announced that the criteria for an influenza pandemic had been met [84]. It is estimated that approximately 200 million cases occurred worldwide [82].

In Europe, there was an initial spring/summer wave of transmission that appeared in most countries, but posed a heavy burden in only a few countries, notably the UK. During this wave, 78% of the reported cases were <30 years of age. Children from 5 to 19 years of age

Table 5. World Health Organization recommended priority groups that should receive influenza vaccination

Pregnant females
Individuals aged >6 months with chronic heart or lung diseases, metabolic or renal disease, chronic liver disease, chronic neurological conditions or immunodeficiencies
Elderly persons over a nationally defined age limit, irrespective of other risk factors
Residents of long-term care facilities for older persons and the disabled
Children aged 6–59 months
Healthcare workers including those who work in facilities that care for the elderly or persons with disabilities

accounted for 46.5% of cases. Only 3.6% of cases were reported to suffer from underlying conditions. A second wave was observed in the early autumn just after the re-opening of schools. This time it affected all countries, with a wave that was seen to progress from west to east across the continent [85].

In total, 2900 official influenza-related deaths were reported by 29 European countries, although it is recognised that this is most probably only a proportion of the true burden of deaths due to the pandemic. In a study on mortality conducted with data from eight European countries, an excess of all cause deaths (1 per 100 000 population) was detected only in school-aged children [86]. It was estimated that 30% of deaths occurred in young healthy people [87]. Clinically, a sizeable number of cases were severely ill presenting with ARDS, an unusual event in seasonal influenza epidemics [87]. In a study of the mortality burden of 2009 H1N1 influenza compared with seasonal influenza, it was found that the 2009 H1N1 pandemic had a 10.6-fold higher mortality impact than inter-pandemic seasons in people aged 5–24 years and 3.8-fold lower impact among people aged over 65 years [88]. Thus, elderly people, who generally account for approximately 90% of deaths during inter-pandemic influenza, were relatively spared. This is probably due to fact that many subjects

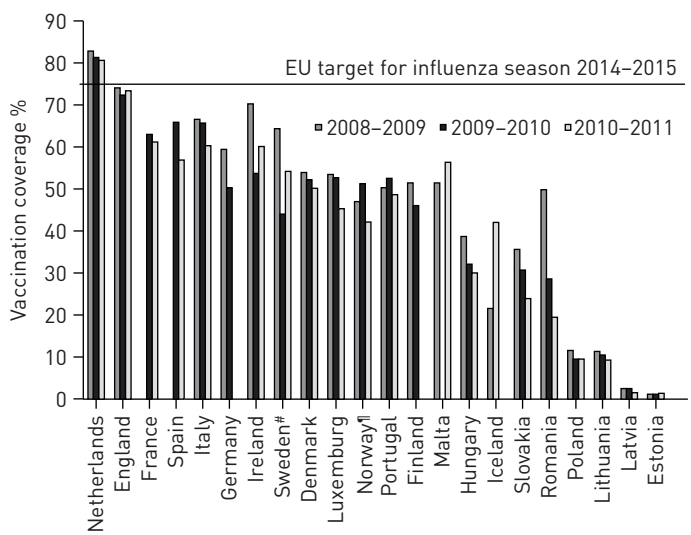

Figure 2. Influenza vaccination coverage among the elderly in 28 European Union countries. #: in Sweden reports were only received for about 60% of the population for the 2009–2010 influenza season; ¶: in Norway coverage results were calculated for adults aged >65 years together with clinical risk groups. Data from [95].

aged ⩾60 years possessed cross-immunity from prior exposure to a presumably antigenically similar influenza virus circulating before the mid-1950s, ensuring that many older people in Europe had some prior immunity [89]. Although many older people appeared to be protected those that were not showed the highest case fatality rates of any age group [90]. Pregnancy, immunosuppression, chronic respiratory conditions and obesity were identified as risk factors for severe disease [57]. In an Italian study, the costs attributable to the 2009 pandemic in Italy were estimated to range from €1.3 to €2.3 billion [91]. In a Greek study on the costs of hospitalisations for H1N1 infection, the authors found that overall, costs were higher for H1N1-positive patients (€610 117.72) than for H1N1-negative patients (€464 923.59) [92]. Excess costs were mainly attributable to the protection measures used and the prolonged hospitalisation in ICUs.

Vaccination coverage

WHO recommendations for the Regional Office for Europe indicate target groups that should undergo influenza vaccination due to higher risk of influenza complications [93]. These are summarised in table 5. In December 2009, the European Council of Ministers unanimously recommended that EU member states adopt and implement national action plans to achieve 75% vaccination coverage in all at risk groups by the winter season 2014–2015 [94]. The European Centre for Disease Prevention and Control committed and funded the VENICE (Vaccine European New Integrated Collaboration Effort) project to collect, share and disseminate information on national immunisation programmes throughout Europe. Through the VENICE network, information was gathered from 29 EU member states regarding national influenza immunisation policies for the influenza seasons 2008–2009, 2009–2010 and 2010–2011 [95]. All of the 29 responding EU countries had influenza vaccine recommendations for the elderly. Vaccination was recommended for those aged >65 years of age in 20 countries, for those aged >60 years in four countries, for those aged >59 years in one country, for those aged >55 years in two countries and for those aged >50 years in two countries. Among the responding countries, vaccination coverage for the elderly reached the target of 75% only in the Netherlands (fig. 2). Some eastern Europe countries had coverage rates as low as <2%. In all 28 countries influenza vaccination was recommended for patients with chronic pulmonary, cardiovascular, renal, haematological or metabolic disorders, and immunosuppression. Vaccine coverage among clinical risk groups ranged from 29% to 80%.

Vaccination for pregnant females was recommended in 23 out of 28 countries. Coverage for pregnant females ranged between 2.4% and 74.8%. Influenza vaccination was recommended for healthcare workers in 26 out of 28 countries. Vaccination coverage among healthcare workers ranged from 12% to 98%.

Conclusion

LRTIs such as pneumonia and influenza continue to pose a considerable threat in Europe in terms of morbidity, mortality, use of healthcare resources and economic impact. Data on the incidence of pneumonia in Europe are still fragmentary due to the limited capacity of individual countries to furnish national epidemiological information. Studies conducted both in northern and southern Europe indicate that hospitalisation rates from CAP are increasing. Data from different European countries confirm very low mortality rates for CAP patients

treated as outpatients, with higher rates for patients admitted to hospital wards and the ICU. In-hospital mortality rates appear to be somewhat higher in eastern European countries.

In recent years, various European networks have been set up to ensure influenza diffusion surveillance, vaccine efficacy and coverage, and monitoring of excess mortality due to the disease. European influenza vaccination coverage rates are still below standards recommended by the WHO and the EU.

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Interstitial lung diseases

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The interpretation of epidemiological studies of interstitial lung diseases (ILD) must take into account methodological issues that may impact results: changes in the classification of ILD and of diagnosis criteria, particularly for idiopathic pulmonary fibrosis; the broad or narrow definition of diseases; and sources. The prevalence and incidence of ILD are around 60–80 cases per 100 000 population and 20–30 cases per 100 000 person-years, respectively. There are four main groups of ILD: sarcoidosis (23–38% of ILD cases); ILD secondary to identified causes (30% of ILD cases); certain rare diseases; and idiopathic interstitial pneumonias (26% of ILD cases), with idiopathic pulmonary fibrosis the most frequent of this last group (19% of ILD cases). The epidemiology of various ILD depends on age, sex, race and smoking habits. For some of them, genetic factors and occupational or environmental factors play a significant role. Epidemiological studies are particularly useful for public health knowledge, optimising diagnosis and better understanding pathogenesis.

Epidemiology of interstitial lung diseases (ILD) is crucial for public health knowledge, optimising diagnosis and better understanding pathogenesis, particularly for idiopathic interstitial pneumonias. Age, sex, race and smoking habits significantly impact ILD epidemiology and diagnosis [1–9]. Moreover, the prevalence of sporadic *versus* familial diseases depends on genetic predisposal, while environmental or occupational exposures may also be essential.

There are more than 200 ILD, and they usually follow a chronic course [2, 5]. Their definition relies mainly on the evidence of diffuse pulmonary infiltration on imaging, which is present in at least 90% of patients. Most patients also have a typical pulmonary function profile with a restrictive pattern and a decreased *D*LCO. Thus, for many diseases, very similar manifestations (clinical, radiological and functional) are shared and aetiological diagnosis may rely on subtle characteristics, with an emphasis on history, computed tomography findings and sometimes pathology. For some diseases, particularly idiopathic interstitial pneumonias, the diagnosis may require multidisciplinary discussion involving pulmonologists, radiologists and pathologists with significant expertise in the field of ILD [10]. The classification and diagnosis of idiopathic interstitial pneumonias was dramatically overhauled

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Table 1. Classification of the main interstitial lung diseases (ILD)

ILD secondary to identified causes
Pneumoconiosis
HP
Drug-induced ILD
CVD-associated ILD
Others
IIP
Chronic fibrosing
IPF
NSIP
Acute/subacute
COP
AIP
Smoking related
DIP
RB-ILD
Rare IIP
LIP
PPFE
Rare histological patterns
Acute fibrosing and organising pneumonia
Bronchiolocentric patterns of interstitial pneumonia
Unclassifiable
Granulomatosis
Sarcoidosis
Rare ILD
Pulmonary Langerhans histiocytosis
Lymphangioleiomyomatosis
Alveolar lipoproteinosis
Idiopathic pulmonary eosinophilia

HP: hypersensitivity pneumonitis; CVD: connective tissue disease and vasculitis; IIP: idiopathic interstitial pneumonias; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; COP: cryptogenic organising pneumonia; AIP: acute interstitial pneumonia; DIP: desquamative interstitial pneumonia; RB-ILD: respiratory bronchiolitis with interstitial lung disease; LIP: lymphoid interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis.

in 2002 [11] and fine-tuned in 2013 [12]. For these reasons, the level of expertise of the people involved in the diagnosis of patients and the criteria of diagnosis need to be taken into account for the interpretation and comparison of epidemiological data.

There are four main groups of ILD: those with an identified cause, sarcoidosis, certain rare diseases and idiopathic interstitial pneumonias (table 1).

Epidemiological studies are still few and have been performed in only limited geographical areas. Some of these studies rely on old criteria for diagnosis while only few rely on recent ones. The most common pitfalls are that studies are not comprehensive or they have limitations concerning the reliability of aetiological diagnosis. Thus, regional or nationwide registries are more likely to be comprehensive for ILD as a whole but less reliable for specific diagnosis, and *vice versa* for studies conducted by pulmonologists' scientific societies. Moreover, as only a limited proportion of patients with idiopathic interstitial pneumonias benefit from a reliable diagnosis in referral centres, caution has to be applied to methodology used.

Table 2. Prevalence and incidence of interstitial lung diseases (ILD)

	Prevalence per 100 000 population	Incidence per 100 000 person-years	% of ILD cases	Comments
All ILD	60–80	20–30		
Sarcoidosis			23–38	
IIP			26	
IPF			19	
ILD secondary to identified causes			30	
CTD-ILD			2.0–12	
HP			0.3–14	
Pneumoconiosis			1.5–13	Organic dusts Mineral dusts
Rare ILD			3.2–6.3	

IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-associated interstitial lung diseases; HP: hypersensitivity pneumonitis.

This chapter will consider the estimation of the incidence and prevalence of ILD as a whole, and then in the case of specific diseases (table 2).

ILD taken as a whole

There is only a limited number of studies devoted to ILD as a whole, sometimes with huge differences in estimations of incidence and prevalence, these differences resulting mainly from different methodological approaches and perhaps also from geographical variation. Most studies were conducted before the introduction of the changes in the most recent classifications, so that the figures concerning ILD as a whole are more reliable than those concerning idiopathic interstitial pneumonias specifically. Moreover, some categories that are dependent on age, particularly for patients under 15 years old, are sometimes not included, while some diseases may not be considered. Often, neither complementary investigations nor criteria used for diagnosis were mentioned.

In a study in New Mexico, USA, published in 1994, the prevalence of ILD was estimated to be 81 cases per 100 000 males and 67 per 100 000 females, while the incidence was 32 and 26 per 100 000 person-years, respectively [2]. In a recent Turkish study conducted between 2007 and 2009, relying on the consensus criteria of 2002, the incidence of ILD was very similar, at 24.7 per 100 000 person-years for males and 27 per 100 000 person-years for females [5]; this study showed evidence of a slight preponderance in females, contrary to that of COULTAS *et al.* [2]. By contrast, the incidence of ILD was found to be dramatically lower in other studies: 4.63 and 7.6 per 100 000 person-years in a Greek study and a Spanish study, respectively [4, 9]. The studies from New Mexico and Turkey are probably more comprehensive, as suggested indirectly by a UK study concerning both idiopathic pulmonary fibrosis (IPF) and sarcoidosis, showing incidences of 4.5 and 5 per 100 000 person-years, respectively [13], these two relatively predominant diseases representing between one third and one half of all ILD cases, validating an incidence of all ILD of 20–30 per 100 000 person-years.

The mean age of patents with ILD is estimated to be between 51 and 69 years [2–5, 9, 14]. The females/males ratio varies between 1/1.15 and 1.2/1 [4, 5, 8, 9]. Interestingly, in the

Turkish study, the use of the 2002 classification, and both the specification of diagnostic criteria and the validation of diagnosis by experts, make the estimation of the contribution of specific diagnoses particularly reliable. In this study, sarcoidosis was the most frequent disease, accounting for 38% of ILD cases, before ILD secondary to an identified cause (collagen vascular diseases, pneumoconioses, hypersensitivity pneumonitis and drug-induced diseases) in 30.4% and idiopathic interstitial pneumonias in 26% [5]. IPF was the second most common specific diagnosis after sarcoidosis, at 19% [5]. As expected, patients with sarcoidosis tended to be younger and patients with IPF older [5]. The females/males ratio was clearly higher than 1 in sarcoidosis and clearly lower than 1 in IPF.

Epidemiology of specific ILD

Most available information concerns sarcoidosis and IPF, which are the most frequent among ILD. Data concerning some diseases, like hypersensitivity pneumonitis or silicosis, depend on occupational and environmental exposure, and may be variable from country to country.

Sarcoidosis

Many studies of sarcoidosis have been performed in several countries. Some studies relied on systematic radiographic screening or on systematic computerised registration at the general practitioners' level. The disease is global but with significant variations according to age, race and geography, and to a lesser extent, sex and smoking habits [15–21]. Sarcoidosis is usually the most prevalent disease, with some exceptions, and often the most incident. In most series concerning particularly, but not exclusively, Caucasians, the incidence is around 3.5–10.9 per 100 000 person-years, but either very low or far higher figures (from 1 to 35.5 per 100 000 person-years) may be observed (table 3). The relative prevalence of sarcoidosis among patients with ILD varies from 23% to 38% (table 2). Sarcoidosis is most frequent in patients between 25 and 45 years of age but a second peak of incidence may be seen after menopause in females, at least in Europe and Japan [16, 21]. Thus, sarcoidosis is by far the most frequent ILD for patients under 45 years of age. However, sarcoidosis very rarely occurs before the age of 15 years [22] or after 70 years. In African Americans, sarcoidosis presents several specific features: the incidence is higher (3.5-fold), and the disease is more often severe and multivisceral [18, 23]. Sarcoidosis is very rare in Japan, but cardiac and ocular localisations are particularly frequent. Sarcoidosis is less frequent in smokers according to

Table 3. Incidence and prevalence of sarcoidosis in most studies

	Most studies	Extremes	Variation factors
Incidence per 100 000 person-years	3–10.9	1.05–35.5	Increased incidence Black subjects Female subjects Age 25–45 years Studies from northern Europe Decreased incidence Age <15 or >70 years Studies from Japan
Prevalence per 100 000 population	10–20	4.7–64	

several studies [17, 20]. Interestingly, while most often sporadic, sarcoidosis may be familial, usually in 3.6–9% of cases, with the greatest increase in risk (4–6-fold) in siblings of index cases [24]. Homozygotic twins of index cases are at a very high risk (80-fold), suggesting that genetic factors play a role in two thirds of the occurrence of the disease [25]. Exposure to musty odours, insecticides and metal processing industries might be risk factors [17]. Recently, two very well designed studies have shown that mortality was significantly increased in sarcoidosis, mainly for people over 55 years of age [13, 26]. The incidence of mortality attributable to sarcoidosis has also been shown to have increased during the last few decades [26].

Idiopathic interstitial pneumonias

In the 2002 classification, the main subgroups of idiopathic interstitial pneumonias were individualised, the most frequent being IPF [11]. In the 2013 revision of the classification, most entities were confirmed, with nonspecific interstitial pneumonia (NSIP) upgraded from provisory to a confirmed entity, and entities being regrouped as fibrosing (IPF and NSIP), acute or subacute (cryptogenic organising pneumonia (COP) and acute interstitial pneumonia), or secondary to smoking (desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis with interstitial lung disease (RB-ILD)). Moreover, a subgroup of rare entities, including lymphocytic pneumonia and pleuropulmonary fibroelastosis, was created [12].

Methodological issues

Five factors need to be taken into account: first, the changes of the idiopathic interstitial pneumonia classification, particularly in 2002 [11], with the individualisation of NSIP; second, the changes in IPF diagnosis in 2000 [27] and then 2011 [10], with an emphasis on the probability of the diagnosis and the need for a multidisciplinary diagnosis; third, in some studies based on registries, the notion of a "broad" and a "narrow" definition of IPF based on the investigations performed; fourth, checking or not of the diagnosis files; and finally, sources varying a lot, from national or regional registry databases, to questionnaire-based sources, to analysis of healthcare databases and, too rarely, a combination of two methods, allowing a capture–recapture control. Studies on the epidemiology of IPF have been impacted by both changes in the idiopathic interstitial pneumonia classification [11] and IPF diagnosis criteria [10, 27], and by the methodology used. Before 2000, IPF diagnosis relied mainly on pathology, and encompassed both IPF *sensu stricto* and some entities that were further individualised, like NSIP. Then, NSIP was individualised as a separate entity and IPF diagnosis could be made without surgical biopsy [27]. In 2011 guidelines [10], the diagnosis of IPF was made simpler with an increasing importance of computed tomography criteria, and multidisciplinary diagnosis was considered crucial. The probability of an IPF diagnosis was considered.

Idiopathic pulmonary fibrosis

Epidemiological data on IPF are very variable according to the sources and study period, and whether a broad or narrow definition of IPF was used [28, 29]. Only half of the available studies were conducted after 2000 and very few used the 2011 diagnostic criteria. The overall prevalence and incidence are 14–63 per 100 000 population and 0.74–17.4 per 100 000 person-years, with variable ranges according to the narrow or broad definition of IPF (table 4) [30, 31]. Recently, the incidence of IPF among US Medicare beneficiaries aged 65 years or older was estimated to be 93.7 per 100 000 person-years, which is particularly high [32]. Interestingly, early detection of ILD in lung cancer screening using low-dose

Table 4. Incidence and prevalence of idiopathic pulmonary fibrosis

	Narrow definition	Broad definition	Variation factors
Incidence per 100 000 person-years	6.8–8.8[#] 0.74–7.4[¶]	16.3–17.4[#]	Increased incidence Age Male subjects Present or past smoking
Prevalence per 100 000 population	14–27.9[#]	42.7–63[#]	

[#]: USA; [¶]: Europe.

computed tomography in smokers (>30 pack-years) aged 54–74 years allowed the discovery of ILD in 2% of the studied population with a progression towards fibrosis for one third of these patients [33].

The mean/median age for IPF diagnosis is between 65 and 74 years, the disease being rarer before 59 years. Except in one study in Norway, IPF is generally more frequent in males than in females (60% and 40% of cases, respectively). Black decedents are less likely and Hispanic decedents more likely than white decedents to have died from IPF [6]. Smoking, either current or in the past, is a confirmed risk factor for IPF, even in familial pulmonary fibrosis [34], and the question remains of whether male sex has an impact or only smoking habits. IPF is most often sporadic but familial cases constitute up to 20% of cases, affecting parents or siblings [35]. Mutations of *TERT* (encoding telomerase reverse transcriptase) or *TERC* (encoding the RNA component of telomerase) and *SPC* (encoding surfactant protein C) may be identified in 20% of familial pulmonary fibrosis. Recently, *MUC5B* (a mucin gene) promoter polymorphism was shown to be linked to IPF, either familial or sporadic, in several studies [36]. In a recent study, a familial history of pulmonary fibrosis was the strongest risk factor for IPF, followed by past smoking, gastro-oesophageal reflux, and exposure to dusts, gases, smokes and chemicals [31, 35]. Certainly, all factors influencing ageing play a role in IPF occurrence [37]. An increase of IPF incidence is suggested by some studies [13, 38] but discrepancies persist with others [39]. Interestingly, in a recent study on patients aged 65 years or older, the incidence of IPF was steady but prevalence increased due to improved survival between 2001 and 2011 [32]. There is a need to estimate IPF epidemiology more accurately, including the impact of some simple factors like sex, geography and time.

Other idiopathic interstitial pneumonias

There is only very scarce information on the epidemiology in idiopathic interstitial pneumonias other than IPF. NSIP is probably the most frequent idiopathic interstitial pneumonia after IPF, despite two studies that probably underestimated it. In the study by Karakatsani *et al.* [4] in Greece, NSIP prevalence among ILD was estimated 2.8%, representing 0.48 per 100 000 individuals, while in the study by Musellim *et al.* [5], NSIP accounted for only 1% of ILD. COP incidence is very variable from one to another study [4, 8, 9]; the study by Musellim *et al.* [5] found figures higher than those for NSIP, accounting for 2.6% of ILD. Other idiopathic interstitial pneumonias are very rare, with DIP accounting for 0.4–0.8% and RB-ILD for 0.07–0.1% of ILD [4, 5]. Unclassifiable ILD, by a broad definition, could represent 10% of ILD [40].

ILD secondary to specific causes

The incidence of ILD secondary to specific causes is evaluated to be 21.3–30% [5, 9]. Connective tissue disease and vasculitis (CVD)-associated ILD and hypersensitivity pneumonitis are often the two main causes among secondary ILD, but with a variable rank depending on exposure to organic dusts. CVD-associated ILD represent 2.1–12.4% of ILD [2–5, 7–9, 14]. Their frequency depends upon that of the respective CVD and of the prevalence of ILD among them. Both rheumatoid arthritis and scleroderma account for more than two thirds of CVD-associated ILD [4]. ILD are the main or an important cause of mortality from rheumatoid arthritis or scleroderma.

The prevalence of hypersensitivity pneumonitis is estimated to be between 1.5% and 13.2% of ILD [2–5, 7–9, 14]. The prevalence of hypersensitivity pneumonitis may be 1–100 cases per 1000 bird breeders and 4–170 per 1000 farmers [41].

The prevalence of pneumoconiosis and other occupational diseases is also variable depending on exposures, from 0.36% to 14% of ILD [2, 4, 5].

The prevalence of drug-induced diffuse lung disease is estimated to be between 1.5% and 3.5% of ILD [2–5, 7–9, 14].

Rare diseases

Rare diseases (pulmonary Langerhans histiocytosis, lymphangioleiomyomatosis, alveolar lipoproteinosis and idiopathic eosinophilic pneumonia) account for 3.2–6.3% of ILD [5, 9]. Pulmonary Langerhans histiocytosis accounts for 0–3.8% of ILD [2–5, 7–9, 14], and occurs most often in smokers between 20 and 40 years of age. Lymphangioleiomyomatosis concerns females in child-bearing age and represents 0.3–0.6% of ILD [5, 42]. Pulmonary alveolar lipoproteinosis is estimated to constitute 0.3–0.5% of ILD [4, 43].

Conclusion

There have been multiple studies on the epidemiology of ILD. However, there is a lack of well-designed studies particularly on idiopathic interstitial pneumonias.

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Chapter 7

Obstructive sleep apnoea in adults

Thorarinn Gislason[1,2] and Ola Sunnergren[3]

Over the past 30 years OSA has evolved from being a very rare disorder, almost solely characterised by loud snoring and daytime sleepiness, to a common systemic disorder with multiple adverse consequences, which affect a substantial percentage of the middle-aged population. Obesity is the strongest risk factor, but not the only pathogenic mechanism. Other important mechanisms include differences in craniofacial dimensions and even lifestyle factors such as smoking, alcohol consumption and sleeping position. Given the systemic effects, there is developing evidence for the role of OSA as an independent risk factor for: excessive sleepiness with increased risk of traffic accidents, hypertension, cardiovascular disease (including atherosclerosis), myocardial infarction, stroke, impaired glucose metabolism, neurodegeneration, and both cancer mortality and incident cancer. Subjects with untreated OSA have increased mortality and are at higher risk when undergoing surgical procedures. The major clinical challenge today is how simplified diagnostic procedures can confirm or reject the possibility of OSA in various situations.

OSA is characterised by repetitive episodes of upper airway obstruction that occur despite continuous respiratory effort. The term apnoea is used when obstruction is total and the term hypopnoea when obstruction is partial. If the individual with OSA has accompanying symptoms (most often excessive daytime sleepiness, fatigue or tiredness) the term OSAS is used.

In the literature, the term SDB is sometimes used interchangeably with obstructive sleep-related breathing disorders. Strictly speaking, the former term also includes other sleep-related breathing disorders, such as central sleep apnoea syndromes. This chapter is confined to epidemiology of OSA and OSAS among adults, describing definitions, diagnosis, prevalence, risk factors, comorbidities and ends with reflections on the clinical importance of the epidemiological findings.

A brief history of OSA

Snoring and sleep apnoea are not new phenomena in humans; writers have long since described snoring in both humans and gods. For example, Hermes was once reproached by the ferryman Charon for lying on the deck snoring instead of helping him row across the river [1]. Writers of the past also mentioned what are today well-described risk factors for

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snoring, such as alcohol, excessive food intake, increased age and supine sleep [1]. In the old Icelandic Snorra- Edda, from Snorri Sturluson, (1179–1241), Thor's travels to Utgard are related. He and his companions were unable to sleep because of an enormous snoring that caused the ground to shake. The next morning, they realised that the snoring came from a giant who was lying on his back. When Thor hits the giant repeatedly on his head with the hammer Mjölnir, the giant only asks if a leaf has fallen on his head.

During the renaissance Shakespeare described an affliction similar to sleep apnoea. In the play *Henry IV*, the character Falstaff is described as being fast asleep, snorting like a horse and then has to catch his breath [2]. Another contemporary writer, Cervantes, used snoring as a characteristic of a good sleep in his work *Don Quixote*. Here, Sancho Panza is described as fat, a good sleeper and a habitual heavy snorer in contrast to the insomniac Don Quixote [3]. Some centuries later, Charles Dickens (1836), in his first novel the *Posthumous Papers of the Pickwick Club* [4], gave a very detailed description of the loudly snoring fat boy, Joe, who suffered from somnolence very much like many of today's patients referred for evaluation of OSA. The term "Pickwick Syndrome" was used in the middle of the 1990s to describe sleep apnoea, often associated with obesity hypoventilation.

From a modern medical perspective, the first known descriptions of OSA date from the second half of the 19th century. In a review in 1984, LAVIE [5] reported that a case of probable mixed sleep apnoea and two cases of probable SDB were described in the medical literature between 1877 and 1889.

After these reports obstructive SDB seems to have been more or less forgotten during the first half of the 20th century. In 1965, GASTAUT *et al.* [6] objectively showed the occurrence of repeated apnoeas in so-called "Pickwickian" patients and in 1967 SCHWARTZ AND ESCANDE [7] were able to show, by cineradiography, that the site where the apnoeas occurred was located in the upper airway.

In the first prevalence studies, OSA was considered to be a very rare disorder. None of the 59 females and 41 males investigated, in a USA-based study, was found to have OSA [8] and among 1001 middle-aged males in England, only three received the diagnosis, OSA [9]. In a letter to the *Lancet* published in 1981, the four authors questioned if OSA really did exist in Scotland [10].

Fortunately for many patients today, with the development of improved diagnostic techniques and the availability of effective treatments [11], OSA has changed from being the very rarely identified disorder it was 30 years ago to a generally acknowledge major disease. In recent decades we have seen a tremendous increase in interest toward OSA and the search term "obstructive sleep apnoea" currently yields almost 20 000 hits on the PubMed website.

OSA: definitions and diagnosis

OSA is characterised by repetitive apnoeas or hypopnoeas during sleep despite continuous respiratory effort. The diagnostic measure most used is the apnoea/hypopnoea index (AHI), which is the total number of apnoeas and hypopnoeas per hour of sleep. When evaluating epidemiological studies on OSA one must keep in mind that the definitions of apnoeas, hypopnoeas, OSA and OSAS have changed over the years.

Apnoeas, hypopnoeas and AHI

The definitions of apnoeas and hypopnoeas, in addition to the equipment used for detection, have been discussed and challenged since they were first introduced. In 1975, GUILLEMINAULT *et al.* [12] defined an apnoea as a cessation of airflow over the nose and mouth lasting at least 10 s. Later it was recognised that even events involving partial obstruction, called hypopnoeas, could have the same negative impact as apnoeas [13]. In 1979, BLOCK *et al.* [14] used the term hypopnoeas to describe respiratory events where the airflow over the nose and mouth only decreased rather than having ceased, as with apnoeas. These authors also used an additional criterion of $\geqslant$4% oxygen desaturation with continued respiratory effort in the definition of a hypopnoea. Nearly two decades later, data from The Sleep Heart Health Study showed that hypopnoeas associated with an oxygen desaturation of 4% were associated with increased prevalence of cardiovascular disease; independent of confounding covariates, in contrast to hypopnoeas with less severe desaturations [15]. In 1988, GOULD *et al.* [16] defined hypopnoeas as events with a reduction in oro–nasal airflow of at least 50% and lasting for a minimum of 10 s.

Historically, many different definitions of apnoeas and hypopnoeas have been in use, but as HIRSHKOWITZ AND KRYGER [17] put it: "having two definitions for a single term is ill advised because it creates ambiguity, confusion, and miscommunication". In 2007, the American Academy of Sleep Medicine (AASM) published The AASM Manual for the Scoring of Sleep and Associated Events [18] with recommendations for the scoring of both apnoeas and hypopnoeas. According to these guidelines, an apnoea shall meet the following criteria if a decrease of airflow ($\geqslant$90% of baseline amplitude) over the nose and mouth for at least 10 s, with $\geqslant$90% of the events duration meeting the amplitude reduction criteria, occurs together with continued respiratory effort throughout the entire period of absent airflow. A hypopnoea shall meet the following criteria: a drop by $\geqslant$30% of baseline in the nasal pressure signal excursions for at least 10 s with $\geqslant$90% of the event's duration meeting the amplitude reduction criteria and finally, the event should be associated with a $\geqslant$4% oxygen desaturation from pre-event baseline. In 2012, the AASM changed their recommendations regarding the definition of a hypopnoea: now the drop in arterial oxygen should be $\geqslant$3% [19], but in other aspects the recommended scoring rules for apnoeas and hypopnoeas were the same as those recommended in 2007.

Definitions of OSA and OSAS

As in the case for the definition of apnoeas and hypopnoeas, there have been many different definitions for OSA and OSAS over the years. In 1999, AASM published recommendations for both the definition and severity classification of OSAS [20]. These recommendations were, as suggested by the name of the article, "Sleep-related breathing disorders in adults: recommendation for syndrome definition and measurement techniques in clinical research", intended for clinical research. For the determination of severity of the disease, the AASM recommended that both subjective sleepiness and the result of overnight monitoring should be assessed and a severity level for both components should be specified. The severity of the syndrome should then be based on the most severe component (table 1).

Notably, these were definitions and criteria for OSAS only (OSA not included). A lower cut-off for the number of obstructive events required was set at five. Since 1999, the AASM have repeatedly revised the criteria for OSA/OSAS in different publications [21–24].

Table 1. Diagnostic criteria and severity classification for OSA/hypopnoea syndrome[#]

Diagnostic criteria[¶]	
A	Excessive daytime sleepiness that is not better explained by other factors
B	Two or more of the following that are not better explained by other factors: choking or gasping during sleep, recurrent awakenings from sleep, un-refreshing sleep, daytime fatigue, impaired concentration
C	Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep
Severity classification	
Sleepiness	Mild: unwanted sleepiness or involuntarily sleep episodes occurring during activities that require little attention. Symptoms produce only minor impairment of social or occupational function Moderate: unwanted sleepiness or involuntarily sleep episodes occurring during activities that require some attention. Symptoms produce moderate impairment of social or occupational function Severe: unwanted sleepiness or involuntary sleep episodes occurring during activities that require more active attention. Symptoms produce marked impairment in social or occupational function
Sleep-related obstructive events	Mild: 5–15 events·h^{-1} Moderate: 15–30 events·h^{-1} Severe: >30 events·h^{-1}

[#]: according to the American Academy of Sleep Medicine [20]. [¶]: the individual must fulfil criterion A or B, plus C.

In 2014, the AASM launched an updated set of criteria for OSA in the third edition of *The International Classification of Sleep Disorders* (herein referred to as ICSD) [24] (table 2). One difference, compared to previous definitions, was that OSA-associated morbidities were included in the criteria, these being: hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, and type 2 diabetes mellitus. Another difference was that methods other than polysomnography (PSG), such as polygraphic recordings (PG), which did not actually record sleep, were accepted. Furthermore, OSA was not clearly differentiated from OSAS, and there was no severity classification was included.

The diagnostic process

As shown in the definitions described previously and especially from a clinical perspective, the diagnostic procedure of OSA can be divided into two parts, the measurement of obstructive respiratory events (the AHI) and the evaluation of symptoms. PSG has been the golden standard for measuring the AHI and include electroencephalogram (EEG), electro-oculogram, chin electromyogram, airflow over the nose and mouth, oxygen saturation and heart rate, under the attendance of trained personnel [23].

A fully attended in-lab PSG recording is highly demanding on resources. However, PSG can also be performed unattended in-lab or at home. Due to the large number of patients referred for OSA evaluation, simpler diagnostic equipment has been developed. Different types of PGs, also called type III portable monitors, are widely used in most European countries [25],

Table 2. Diagnostic criteria for OSA[#]

	Diagnostic criteria[¶]
A	The presence of $\geqslant$1 of the following: 1) The patient complains of sleepiness, non-restorative sleep, fatigue or insomnia symptoms 2) The patient wakes with breath-holding, gasping or choking 3) The bed partner or other observer reports habitual snoring, breathing interruptions or both while the patient is sleeping 4) The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation or type 2 diabetes mellitus
B	PSG or OCST[+] demonstrates: 1) $>$5 events·h^{-1}, predominantly obstructive respiratory (obstructive and mixed apnoeas, hypopnoeas or RERAs) during a PSG or per hour of monitoring at an OCST 2) Respiratory events defined according the most recent version of the AASM manual for the scoring of sleep and associated events [24] 3) RERAs and hypopnoea events based on arousals from sleep cannot be scored using OCST because arousals by EEG criteria cannot be identified
C	PSG or OCST demonstrates: $\geqslant$15 events·h^{-1}, predominantly obstructive respiratory events (apnoeas, hypopnoeas or RERAs) of sleep during a PSG or per hour of monitoring (OCST)

PSG: polysomnography; OCST: out-of-centre sleep testing; RERAs: respiratory-effort related arousals; AASM: American Academy of Sleep Medicine; EEG: electroencephalogram. [#]: according to *The International Classification of Sleep Disorders* [24]. [¶]: A and B, or C satisfy the criteria. [+]: the use of OCST with limited channels (EEG is not usually recorded) is now included in the diagnostic criteria for adult OSA.

and are now also accepted as a diagnostic tool for OSA in the 2014 ICSD [24] (where they are called OCSTs, see table 2). PG does not record EEG, so actual sleep is not recorded, and since the AHI ideally should be calculated from total sleep time, the AHI assessed by PG devices has to be calculated from total recording time or an estimation of sleep time. If only recording time is used as a surrogate for actual sleep, total recording time is at risk of providing a diluted (reduced) AHI.

In a systematic literature review on OSAS published in 2007 by the Scandinavian agencies for Health Technology Assessment [26], the conclusion was reached that manually-scored portable devices that measured airflow, respiratory effort and blood oxygen saturation, had a high sensitivity and specificity to identify different cut-off values of pathologic AHI (from 5 to 15) [26]. Ng *et al.* [27] reported high correlations between AHI obtained by hospital-based PSG and PG (performed simultaneously) in patients with suspected OSAS (both groups had AHI=21). One study found PG to accurately identify patients without OSA [28] and another that PG was highly sensitive compared to PSG to determine presence of OSA when AHI $\geqslant$5 was used as cut-off [29].

Daytime sleepiness is regarded as the cardinal symptom of OSAS. In most settings, the clinical evaluation of sleepiness is complemented by questionnaires. The Epworth Sleepiness Scale (ESS) is the questionnaire most used in both clinical practice and research to evaluate OSA-related daytime sleepiness. The ESS is a self-administered questionnaire focusing on

subjective reports of the likelihood of falling asleep or dozing during eight different common daily life situations [30]. The ESS combines a retrospective and forward-looking approach; however a possible limitation is that the scale primarily reflects the lifestyle from 25 years ago with, for example, no mention of sleepiness associated with work at a computer. Questionnaires are thought to be sensitive to motivation, recall bias, education level, and fatigue [31]. Sleepiness can also be evaluated through objective testing. Objective tests are time consuming, demand sleep-laboratory facilities, and are not used in routine clinical practice. Different methods for measuring daytime sleepiness are not interchangeable [31, 32].

Prevalence

OSA is highly prevalent in the general adult population and more common in males than in females [33–35]. Furthermore, and explained by the fact that OSA often is asymptomatic, there is a large difference in prevalence rates between OSA and OSAS, with OSA being more prevalent than OSAS. In clinical samples (with subjects referred for evaluation of OSA), the picture is different and symptoms, *e.g.* sleepiness, are a common complaint [36, 37]. Table 3 summarises studies on the prevalence (based on PSG recordings) of OSA and OSAS in general populations.

The prevalence of OSA has varied greatly in larger, recent studies; 9–58% for AHI $\geqslant$5 and is most often higher than 10% for AHI $\geqslant$15. OSA prevalence is higher among males and increases with age (table 4). In the most recent epidemiological study, on a random sample of 399 Swedish females, the highest prevalence figure for OSA seen among females (50% with AHI $\geqslant$5) was reported [40]. As discussed by the authors of this article, some of the differences can be explained by different inclusion criteria, different populations when the study was performed, and the use of different definitions for apnoeas, hypopnoeas and OSAS. Notably, OSA is even more prevalent in populations with overweight [41] and with cardiovascular disease [42]. Most published studies reported a progression of OSA over time and that progression was mainly dependent on weight gain. However, there are also some studies reporting a progression in the absence of weight gain (table 5).

Table 3. Prevalence of OSA and OSAS, based on polysomnography (PSG) studies in general populations

First author [ref.]	Country of study	Males/ females n	Age range years	OSA males/ females			OSA males/ females
				AHI $\geqslant$5	AHI $\geqslant$10	AHI $\geqslant$15	
YOUNG [33]	USA	352/250	30–60	24/9	15/5	9/4	4/2
BIXLER [38]	USA	741/1000	20–100			7.2/2.2	3.9/1.2
DURÁN [34]	Spain	1050/1098	30–70	26/28	19/15	14/7	3.4/3
YOUNG [39]	USA	2648/2967	39–99	33/26		25/11	
HRUBOS-STRØM [35]	Norway	284/234	30–65	21/13		11/6	
FRANKLIN [40]	Sweden	/399	20–70	/50		/20	/17

Data are presented as percentages, unless otherwise stated. For the different definitions used for apnoea, hypoapnea and OSAS in each study, refer to the reference given.

Table 4. Prevalence of apnoea/hypopnoea index (AHI) according to age and sex

First author [ref.]	Age years								
	20–44	30–39	40–49	45–54	<50	>50	50–60	55–70	60–70
Young [33]									
AHI ⩾5									
Males		17	25				31		
Females		6.5	8.7				16		
AHI ⩾15									
Males		6.2	11				9.1		
Females		4.4	3.7				4		
Durán [34]									
AHI ⩾5									
Males		9	25.6				27.9		52.1
Females		3.4	14.5				35		46.9
AHI ⩾15									
Males		2.7	15.5				19.4		24.2
Females		0.9					8.6		15.9
Hrubos-Strøm [35]									
AHI ⩾5									
Males					18	23			
Females					10	16			
AHI ⩾15									
Males					9	13			
Females					4	8			
Franklin# [40]									
AHI ⩾5	24			56				75	
AHI ⩾15	4.2			17				43	

#: females only.

Risk factors for OSA in epidemiological studies

Age

OSA prevalence increases with age (table 5). Several potentially age-dependent factors may be in play: deteriorative changes in the structure of muscles and soft tissues, decreases in muscular tone during sleep [57], or decreases in respiratory effort during obstructive events [58]. Furthermore, as reviewed by Punjabi [59], other factors that may be involved include: the increased deposition of fat in the parapharyngeal area, lengthening of the soft palate, and changes in body structures surrounding the pharynx. A study of 48, otherwise healthy, males and females [60] showed an age-dependent decrease in the response to negative pressure, increased deposition of parapharyngeal fat, a lengthening of the soft palate, and a change in the bony shape surrounding the pharynx, all factors predisposing pharyngeal collapse.

Male sex and female menopause

In general, males seem to be more vulnerable than females to develop OSA, and epidemiologic studies show higher prevalence rates in males than in females with a ratio of 2:1 to 3:1 [59]. Differences in upper airway shape, craniofacial morphology, pattern of fat

Table 5. OSA progression over time

First author [ref.]	Subjects n	Age years		AHI		RDI		ODI		BMI		Main finding
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	
Mason [43]	32	70.3	4.6			16.1	17.0			No data	No data	Sleep apnoea indices did not increase over time
Phoha [44]	11	65.9	3			3.4	5.5			No data	No data	The respiratory disturbance index showed a significant increase over 3 years
Svanborg [45]	42	55	16[¶]					10.1	20.9	27.1	27.3	Increases in ODIs were significantly correlated with increases in body weight
Sforza [46]	32	51	5.7	52.2	52.2					30.7	31	Weight gain does not contribute significantly to OSAS exacerbation
Hoch [47]												
	23	69.3	3	3.9	8.7					No data	No data	There was no change
	27	81.1	3	5.4	9.2					No data	No data	in sleep apnoea
Pendlebury [48]	55	55.8	77[+]	21.8	33.4					29.7	29.6	OSA has a tendency to worsen in the absence of significant weight gain
Lindberg[#] [49]	29	50	10	2.1	6.8					26.0	26.3	SDB became significantly worse over time
Peppard [50]	690	46	4	4.1	5.5					29	30	Even modest weight control is likely to be effective in managing SDB
Young [41]												
Males	161	No data	8	3.3	6.3					No data	No data	There were significant
Females	121	No data	8	1.5	3.8					No data	No data	increase in mean AHI in all strata of sex, BMI, age, and snoring
Fisher [51]	40	47	5			27	28			28.9	29.4	Untreated OSA patients RDI does not necessarily increase over time

Table 5. Continued

First author [ref.]	Subjects n	Age years		AHI		RDI		ODI		BMI		Main finding
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	
REDLINE [52]												
Males	197	29.5	5			3.7[§]	5.4[§]			25.4	27.7	Longitudinal change in the RDI varies nonuniformly with age sex, and weight
Females	289	33.0	5			2.0[§]	3.0[§]			27.5	29.6	
NEWMAN [53]												
Males	1342	62.1	5			3.4[f]				0.5[f]		Modest changes in weight were related to an increase or decrease in SDB
Females	1626	61.8	5			2.2[f]				0.6[f]		
SAHLMAN [54]	28	50.2	3.9	9.0	22.3					0.9[##]		Mild OSA has a natural tendency to worsen over time
BERGER[#] [55]	160	50.6	5.1	23.0	28.9					29.3	30.1	Only change in BMI and time were significant predictors for AHI change
SILVA [56]												
Males	1385	62.3	5			10.5	13.9			28.7	29.2	A slight increase in severity of SDB was seen over 5 years
Females	1693	61.9	5			6.2	8.4			28.8	29.3	

Data are presented as mean, unless otherwise stated. Study groups were mixed unless otherwise stated. AHI: apnoea/hypopnea index; RDI: respiratory disturbance index; ODI: oxygen desaturation index; [#]: males only; [¶]: months; [+]: weeks; [§]: results given as median; [f]: overall change; [##]: change from baseline.

deposition, and occupational and environmental exposures have been proposed as explanations [39].

Sex differences in OSAS prevalence rates could theoretically be due to differences in the expression of symptoms (*i.e.* that females remain undiagnosed because their symptoms are different from the more studied male population). However, such differences could not be found in a study by YOUNG *et al.* [61] where symptoms of 338 females and 551 males from the Wisconsin Sleep Cohort Study were compared.

The potential role of sex hormones was showed in an epidemiological study where pre-menopausal and post-menopausal females on hormone replacement therapy (HRT) were found to have a lower prevalence of OSA compared to post-menopausal females without HRT [38]. Also, SHAHAR *et al.* [62] reported that HRT in post-menopausal females is associated with a lower prevalence of OSA.

Being overweight

Being overweight is considered as one of the major risk factors for OSA and its progression over time (table 5). The prevalence of OSA in obese clinical patients has been reported to be as high as 50–80% and 60–90% of OSA patients may be overweight [63]. An association between overweight and OSA in the general population has been shown in large epidemiological studies, such as the Wisconsin Sleep Cohort Study [33]. In this study, obesity was found to be a significant risk factor for an AHI $\geqslant 5$, and one standard deviation increase in BMI was associated with a four-fold increase in OSA prevalence [33]. Obesity may compress and/or alter the properties of the upper airway by the deposition of fat tissue [63].

Craniofacial soft- and hard-tissue anatomy

All features of soft- and hard-tissue anatomy that impairs the size of the upper airway may potentially increase its propensity to collapse during sleep. In a large study on 420 patients, enlargement of the oropharyngeal soft tissue structure by lateral narrowing of the pharyngeal wall and enlarged tonsils was associated with an increased likelihood of OSA after adjusting for BMI and neck circumference [64]. The volume of the tongue and the size of the lateral walls were shown to increase the risk of sleep apnoea in a case-control study using magnetic resonance imaging [65]. In non-obese females, a low soft palate, retrognathia, and a uvula that touched the posterior pharyngeal wall in the supine position, were all significant predictors for OSA [66].

Asians appear to show greater restriction in skeletal measurements, including a smaller maxilla, smaller and retro-positioned mandible, and a shorter steeper anterior cranial base [67]. This restricted bony compartment may put them at greater risk for developing OSA if they gain weight, since excess obesity will further exacerbate the anatomical imbalance. However in a recent review on the prevalence of OSA in Asian adults, it was concluded that data is lacking to estimate the burden of OSA [68].

Heredity

Several studies indicate a hereditary component in OSA pathology. REDLINE *et al.* [69] reported a significant familial aggregation of OSA symptoms after adjusting for body weight, age and sex.

In a large Icelandic cohort, the relative risk for OSA was two-fold to three-fold among close relatives and the risk was also significantly increased for non-obese OSA patients [70].

Smoking and alcohol

Smoking is correlated to an increased risk of obstructive SDB [9, 26]. One proposed mechanism is that smoking induces upper airway inflammation and the damage alters the properties of the upper airway, rendering it more susceptible to collapse [59]. Alcohol has a depressive effect on muscular tone and alcohol intake has been shown to increase the AHI and worsen hypoxaemia even in otherwise normal males [71, 72].

Supine sleep

In 1984, CARTWRIGHT [73] reported that the majority of OSA patients had twice the AHI in the supine position when compared with the side positions. This finding was later confirmed in a larger sample where 56% of the patients had position-dependent OSA (defined as a supine AHI twice the non-supine AHI) [74]. The most plausible reason for this discrepancy in severity of OSA between supine- and non-supine sleep is the effect of gravity in the supine position. Gravity predisposes the soft tissues in the upper airway (especially the tongue and mandible) to fall backwards thus narrowing the airway.

Comorbidity in OSA

Hypertension

Many studies have reported a very high prevalence of hypertension among OSA patients independent of conventional risk factors [34, 42, 75]. Others have found OSA associated with an independent risk for developing hypertension in long-term follow-up studies [50, 76].

Randomised placebo-controlled trials have shown that CPAP can reduce 24-h blood pressure in OSA, but the decrease in blood pressure (BP) was small [77]. Longer CPAP treatment per night has been associated with a greater reduction in BP [78, 79]. A greater reduction in BP occurred with increasing OSA severity, greater frequency of arousals during diagnosis of OSA, and greater adherence to treatment, but with no significant effect of subjective sleepiness reported at baseline [80].

A recent review reported that both diurnal systolic and diastolic blood pressure were significantly reduced only in studies utilising a sham positive airway pressure control, studies with treatment duration $\geqslant$4 weeks, studies with mean age at baseline of $<$50 years, studies with mean ESS at baseline $\geqslant$11/24, and studies with mean AHI at baseline $\geqslant$30 [81].

Cardiovascular disease

Recent reviews describe a high prevalence of OSA in populations with hypertension (30–83%), heart failure (12–53%), ischemic heart disease (30–58%) and stroke (43–91%) [42, 82]. The evidence for a link between OSA and cardiovascular disease comes from epidemiological studies, clinical cohorts of sleep apnoea patients and from randomised treatment trials of OSA treatment efficacy as reviewed by PACK AND GISLASON [83] in 2009. In their article they discuss the urgent scientific challenge in separating the effects of OSA from those of obesity and of

learning how much of the cardiovascular consequences of obesity can be mediated by OSA, independently of obesity and other known risk factors. The authors state that both obesity and OSA can activate the same pathogenic mechanisms with the same end-points (*i.e.* insulin resistance, hypertension and cardiovascular disease). The chronic intermittent hypoxia and sleep fragmentation with arousals in OSA may initiate oxidative stress, inflammatory pathways and sympathetic activation, which in turn leads to increased levels of fatty acids, adipokines, and endothelial dysfunction, all shared pathogenic mechanisms with obesity [84].

In a follow-up study (>3 years), OSA was found to increase the risk for stroke and all-cause mortality independent of other cardiovascular- or cerebrovascular risk factors [85]. MARIN *et al.* [86] reported similar findings when they compared fatal- and non-fatal cardiovascular events (mean follow-up 10.1 years) in healthy males, snoring males, males with untreated mild/moderate OSA, males with untreated severe OSA and males with OSA that were treated with CPAP. Their results showed that untreated severe OSA increased the risk for both fatal- and non-fatal cardiovascular events and that CPAP treatment reduced this risk.

SHAH *et al.* [87] performed an observational cohort study on patients aged $\geqslant$50 years and had been referred for OSA evaluation. The group found that an AHI $\geqslant$5 at baseline increased the risk for death from cardiovascular causes during follow-up (mean 2.9 years). The results were significant even after adjustment for other traditional cardiovascular risk factors. In a prospective observational cohort study on females referred to a sleep clinic with suspected OSA, CAMPOS-RODRIGUEZ *et al.* [88] found that severe OSA was associated with cardiovascular death also in females and that CPAP treatment seemed to reduce this risk.

Longitudinal studies with samples from general populations show the same picture. MUNOZ *et al.* [89] studied the risk of ischemic stroke in elderly patients with OSA (n=394, follow-up time 6 years) and found that severe OSA (AHI $\geqslant$30) increased the risk for stroke independently of other known risk factors. Prospective data (follow-up time 8 years) from the Sleep Heart Health Study with 5422 participants from the general population, show that moderate and severe OSA at baseline were associated with a three-fold increased risk of a stroke in males and also that females with AHI >25 had an increased risk for a stroke [90]. Data from the same study (median follow-up time 8.7 years) showed that (after adjustment for risk factors) OSA was a predictor of incident coronary heart disease in males aged $\leqslant$70 years, but not in older males or females [91]. Data from this study also showed that OSA predicted incident heart failure (again only in males). Prospective data from the Wisconsin Sleep Cohort Study also showed an association between OSA and the incident of a stroke within 4 years [92].

Insulin resistance, diabetes and the metabolic syndrome

There are both cross-sectional clinical and general population-based studies that have reported an association between the presence and severity of OSA and glucose intolerance, insulin resistance and diabetes [93]. In a longitudinal community-based study that involved Swedish males with a mean follow-up of 11 years, it was found that an oxygen demand index (ODI) >5 at baseline was a predictor for developing diabetes (after adjusting for age, baseline BMI, change in BMI, hypertension and CPAP use) and all variables of SDB were associated with a deterioration of insulin resistance [94].

Treatment trials with CPAP have indicated an improvement in glucose metabolism, especially among non-obese subjects [95]. A recent meta-analysis of five randomised, controlled trials that evaluated the effect of CPAP on insulin resistance showed a favourable effect of CPAP on insulin resistance in 244 patients with OSA without diabetes [96].

Accidents in traffic and at work

Sleepiness and falling asleep at the wheel are common causes of traffic accidents. Since one major consequence of OSA is sleepiness and the prevalence of OSA is high in both the general population and especially in commercial drivers [97], the question of the possible association between driving safety and OSA is of great importance.

In a review by TREGEAR *et al.* [98], 18 articles were analysed for OSA and crash risk. The main conclusion was that untreated sleep apnoea is a significant contributor to motor vehicle crashes and that crash predicting characteristics might include BMI, AHI, nightly oxygen saturation, and possibly daytime sleepiness. However, not only is a higher BMI in OSA a risk factor for crash, but also BMI alone. Regarding sleepiness and crashes, eight articles were included using the ESS and none could confirm that increased risk correlated to higher ESS scores.

OSA subjects are also at increased risk for work-related accidents. Subjective work performance has been shown to be lower in snorers and OSAS subjects compared to the general population [99], and furthermore, subjects referred for evaluation of SDB were twice as likely to become involved in an occupational accident over a 10-year period compared with the general population [100]. LINDBERG *et al.* [101] report from a community-based study using questionnaires (follow-up 10 years) that sleepy snorers, in contrast to non-sleepy snorers and sleepy non-snorers, had an increased risk for occupational accidents.

Neurodegeneration and OSA

Growing evidence suggests that chronic inflammation, as found in OSA, also plays a critical and intimate role in Alzheimer's pathology [102]. To what extent OSA, with its intermittent hypoxia and systemic inflammation, may play a role in the development of neurodegeneration or Alzheimer's Disease is not currently known [103]. In a large epidemiological study where 1,793 participants were screened for OSA, there was an association between mild cognitive impairment and sleep disturbances, but not with OSA [104].

Cancer and OSA

Several population-based studies have shown, in long-term follow-up settings, that there is an increased risk for cancer, both incidence rate and mortality, among OSA patients compared to non-apnoeic subjects [105–107]. There have also been reports on several biological mechanism, possibly explaining this relationship [108, 109], and importantly, effective CPAP treatment has been associated with decreasing levels in circulating leukocyte gene expression suggesting potentially novel mechanisms linking OSA with neoplastic signatures [110].

Is OSA causing nocturnal gastro-oesophageal reflux and respiratory symptoms?

In epidemiological studies, nocturnal gastro-oesophageal reflux (nGER) is often related to both OSA and respiratory diseases and symptoms [111–114]. A substantial number of

subjects in the general population seem to be suffering from nGER on the basis of OSA and nGER is significantly associated with asthma and/or poorly defined respiratory symptoms like wheeze, chronic cough and bringing up phlegm in the morning [113]. However, a causal relationship between nGER, OSA and respiratory illnesses is not proven in randomised, controlled trials involving effective OSA treatment.

Perioperative complications

In a recent review of OSA and perioperative complications, numerous studies are cited where the undiagnosed OSA individual is at a greater risk [115]. Recently, it was also shown that preoperative OSA was a strong risk factor for postoperative atrial fibrillation and a longer hospital stay [116].

Conclusion

With the high prevalence of OSA in mind, especially in populations with cardiovascular disease, there is a need to facilitate the identification of patients with undiagnosed OSA. The main question is not if the "true" OSA prevalence is 10%, 20% or some other percentage in the general middle-aged population. OSA is highly prevalent, and the possibility of OSA has to be considered seriously in a variety of clinical situations. An obvious problem is that many undiagnosed OSA patients only present small or even no classic OSA symptoms. These patients still have an increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents, and diminished quality of life. If a patient with OSA is not diagnosed, he or she will obviously not benefit from the effective treatment available and risk adverse health consequences. Therefore, more efficient screening methods are urgently needed, but until then at least patients who snore and/or are obese should be considered to have OSA until shown otherwise.

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Chapter 8

The economic burden of respiratory diseases: lung cancer and oxygen treatment

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Cost analyses have become an increasingly important consideration in healthcare decisions over the last decade. This is especially the case in the field of respiratory diseases, the most serious of which have a major impact on public health. This review focuses on the cost of lung cancer (overall costs, costs at different disease stages, and the use of chemotherapy and targeted therapies) and oxygen therapy. The aim is to provide the clinician with data complementary to clinical outcomes, and to expand their knowledge of the economic impact of these major respiratory diseases and conditions.

Health economic assessment studies have become more numerous in recent years, with the aim of assisting with clinical decision-making without undermining the doctor–patient relationship. It is particularly important to estimate the societal impact of respiratory diseases in what is currently a difficult economic environment. This will provide clinicians with an additional viewpoint that they must understand, master and integrate into their daily practice [1–3]. The economic burden of a particular disease incorporates several dimensions (fig. 1): 1) treatment-related toxicity, which can lead to intolerable adverse effects; 2) efficacy, which remains the primary determinant of therapeutic choices; and 3) quality of life, which has become a recognised standard of judgment.

The Forum of International Respiratory Societies has released a report on the impact of respiratory disease [4]. It identifies five conditions (asthma, COPD, acute respiratory infections, TB and lung cancer) that largely account for the global burden of respiratory diseases.

The present review is limited to lung cancer and oxygen treatment, diseases and conditions that have a major impact in Europe.

Burden of lung cancer

Global costs

In European countries, in 2009 [5], lung cancer was the costliest malignancy, at €18.8 billion, representing 15% of all cancer-related costs, which totalled €126 billion in

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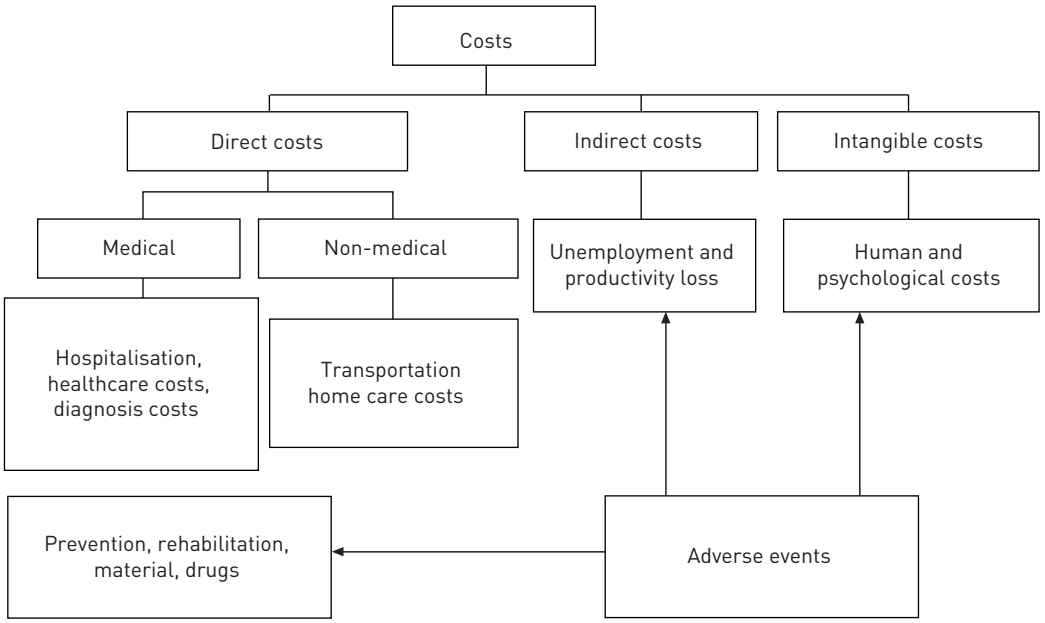

Figure 1. The different types of costs included in economic analyses.

2009; €43 billion were due to lost productivity and early death. This value is probably underestimated [5].

In France [6], the global direct cost has reached more than 2009 €7 billion. Among them, treatments accounted for 20% of drug expenditures in hospitals. The cost of lung cancer treatment represented 2.1% of all health care French expenditures [7]. In 2008, in Northern Ireland [8], the major cost component was patient stays. Toxicities (chemotherapy induced) are probably another cost driver from a German perspective [9].

The principal studies in the area are described in the table 1 [10–16, 18–27]. They have been separated into studies conducted in the European Union and those conducted in North America. Most studies provided an average cost per patient. Only one included a model predicting costs for the period 2005–2020 [10]. Kutikova *et al.* [24] only provided the total costs per patient and not the overall cost of the disease. One study [25] concerned only persons over 65 years of age while Cypriano *et al.* [26] compared average costs for patients under and over 65 years. One study focused on small cell lung cancer [28]. According to treatment choice, the global costs were €16 644 to €18 171 (2002 euros). Unfortunately, different cost analyses are not always comparable, owing to differences in healthcare systems, data recording, *etc.*

Stage I and II NSCLC

Casali and Walker [29], adopting the viewpoint of UK hospitals, showed that the cost of using the operating room was higher with video surgery but that the costs of other parts of the stay were lower, resulting in a lower overall cost. Ramos *et al.* [30] reported that in 2012, the total cost of video surgery was €11 934.13 compared with €14 145.57 for thoracotomy. No studies have examined the economics of adjuvant chemotherapy in Europe.

Table 1. Studies assessing the cost of NSCLC management in the European Union and North America

First author [ref.]	Country	Healthcare systems	Epidemiological approach	Perspective	Currency/ year	Total costs	Costs per patient		Direct costs %	Indirect costs %	Actualisation costs
							Lung cancer	NSCLC			
European Union											
Koopmanschap [10]	Netherlands	Public and private insurance	Incidence and prevalence	Not specified	Million DFL/1988	136.10	DFL 4598		100		No
Wolstenholme [11]	UK	National Health Service	Incidence	Hospital	£/1993			£9280	100		Yes (6%)
Weissflog [12]	Germany	Public social insurance	Incidence	Payer	Billion DM, 1996	4246.10	DM 150 582		11	0.89	No
Braud [13]	France	Public social insurance	Incidence	Hospital	€/2001		€12 518	€13 970	100		No
Chouaïd [14]	France	Public social insurance	Incidence	Payer	Billion US $/1999	439.10		US $18 153–23 041	100		No
Vergnenègre [15]	France	Public social insurance	Incidence	Payer	Million €/1999	612.10	€25 644	€20 543–30 424	100		No
Pompen [16]	Netherlands	Public and private insurance	Prevalence	Payer	€/2005			€31 187	100		No
Isla [17]	Spain	Public insurance	Incidence	Payer	€/2009			€11 301–32 754	100		No
North America											
Evans [18]	Canada	Public social insurance	Incidence	Payer	CA $/1988			CA $5262–12 039	100		No
Evans [19]	Canada	Public social insurance	Incidence	Payer	Million CA $/1988	221.10	CA $14 136	CA $13 314	100		No
Berthelot [20]	Canada	Public social insurance	Incidence	Payer	Million CA $/1995	83.10–138.10		CA $17 709–27 713	100		No
Evans [21]	Canada	Public social insurance	Incidence	Payer	Million CA $/1988	221.10	CA $14 136	CA $13 313	100		No
Evans [22]	Canada	Public social insurance	Incidence	Payer	Million CA $/1993	70.10–90.10		CA $16 949–20 316	100		No
Evans [23]	Canada	Public social insurance	Incidence	Payer	Million CA $/1993	62.10–73.10		CA $14 945–16 600	100		No
Kutikova [24]	USA	Public and private insurance	Incidence	Payer	US $/2004		US $109 085		100		No
Yabroff [25]	USA	Private insurance	Register and model	Payer	Million US $/2004	4238		US $54 665–61 646	100		No
Cipriano [26]	USA	Public and private insurance	Register	Payer	US $/2010		US $76 539–164 768	US $60 533–130 131	100		Yes

DFL: Dutch florin; £: pound sterling; DM: Deutsche Mark; €: euro; US $: US dollar; CA $: Canadian dollar.

Locally advanced NSCLC

Economic analyses of locally advanced NSCLC are rare (table 2). A French study [31] used data from a randomised trial to study cost minimisation between sequential and concomitant chemoradiotherapy. The results favoured concomitant treatment. A Belgian study [32] based on a Markov model compared early *versus* later continuous hyperfractionated accelerated radiotherapy. The cost per quality-adjusted life-year (QALY) ranged from €9164 to €11 576 (2000).

Advanced-stage NSCLC

First-line treatments

It is now clear that chemotherapy is cost-effective when compared with supportive care [18]. The table 3 shows studies performed in European Union [33–38]. A comparison of platinum-based doublets showed no superiority of any particular combination, except perhaps for platinum–gemcitabine [39], from a European perspective.

Maintenance treatments

All previous reports have reached the same conclusion that maintenance treatments are too expensive for the majority of countries [40–45]. For instance, in Switzerland, the ratio was €106 222 per QALY. For targeted therapy, NICE consider that erlotinib was not cost-effective [44]. However, another author found a ratio of less than €30 000 in several European countries. The analysis was based on SATURN trial [45]. All the probabilities were above 90.0% in five European countries. The same result was found in patients with stable disease included in the SATURN trial [46].

Second-line treatments

VERGNENEGRE *et al.* [47] analysed quality of life and utility based on the data of NAFEES *et al.* [48] and found that the cost per QALY was €22 798 with docetaxel and €40 980 with pemetrexed. Both values are acceptable for the French healthcare system. SCHWANDER *et al.* [49] found a cost difference in favour of erlotinib because of the small number of adverse effects and the lower costs of drug administration (fig. 2).

Targeted therapies

Gefitinib [50] was the first tyrosine kinase inhibitor to be approved for the treatment of NSCLC (table 4). Early data showed an average treatment cost per patient of approximately US $46 000 during the first 2 years [51]. CHOUAID *et al.* [55] performed a model-based study of compassionate-use gefitinib therapy in France (between 2002 and 2004) based on data for

Table 2. Main economic studies of locally advanced lung cancer

First author [ref.]	Country	Year	Perspective	Intervention	Methods/ analyses	Results
VERGNENEGRE [31]	France	2002	Payer	CON *versus* SEQ RT-CT	Prospective based on RCT	€15 245 per CON €16 074 per SEQ
LIEVENS [32]	Belgium	2000	Society	CHART delayed	CUA based on literature	€9164 per LYG €11 576 per QALY

CON: concomitant; SEQ: sequential; RT-CT: radiochemotherapy; CHART: continuous hyperfractionated accelerated radiotherapy; RCT: randomised controlled trial; CUA: cost–utility analysis; €: euro; LYG: life-year gained; QALY: quality-adjusted life-year.

Table 3. Main economic studies for the use of chemotherapy in first line advanced NSCLC

First author [ref.]	Country	Year	Currency	Perspective	Intervention	Methods/ analyses	Results
SACRISTAN [33]	Spain	1997	Pesetas	Payer	GP *versus* VP	Prospective CMA based on RCT	Cost per patient GP: 584 523 VP: 589 630
LEES [34]	UK	2000	£	National healthcare system	GP *versus* PC, PCar, DC, ViP	Retrospective CEA based on three RCTs (three chemotherapy regimens)	GP *versus* PC: -3506 GP *versus* Pcar: -2907 GP *versus* DC: -242 GP *versus* Vip: -571
NEYMARK [35]	Netherlands	2002	€	Insurance	GP *versus* PC, PG	Prospective CMA based on RCT	GP *versus* PC: -2062 GP *versus* PG: -3429
PIMENTAL [36]	Portugal	2003	€	Payer	GP *versus* ViP, PCar, DC, PC	Retrospective CMA based on two RCTs	Cost per patient: GP: 7083 PCar: 10 008
NOVELLO [37]	Italy	2003	€	National healthcare system	GP *versus* PCar, ViP	Retrospective CMA based on two RCTs	Cost per patient: GP: 8094, PCar: 11 203 ViP: 9320
RUBIO-TERRÉS [38]	Spain	2000	€	Payer	PC *versus* PCar, DC	Retrospective CMA based on RCT	Cost per patient: PC: 8205, PCar: 8522 DC: 6418

£: pound sterling; €: euro. GP: gemcitabine–cisplatin; VP: VP16–cisplatin; PC: paclitaxel–cisplatin; PCar: paclitaxel–carboplatin; DC: docetaxel–cisplatin; ViP vinorelbine–platinum; PG: paclitaxel–gemcitabine; CMA: cost minimisation analysis; RCT: randomised controlled trial; CEA: cost effectiveness analysis.

106 patients. The total cost for each of these patients was €40 000 ± 20 729, gefitinib representing about 10.7% of the overall cost (€4241 ± 1424). However, this study included only highly selected patients. HORGAN *et al.* [52] based their study on the dataset of the INTEREST (Iressa NSCLC Trial Evaluating Response and Survival against Taxotere) clinical trial. In this cost utility study based on prospective data, the marginal cost effectiveness of gefitinib *versus* docetaxel was CA $5161, which was considered acceptable for the North American healthcare system. Adverse effects and quality of life also favoured the use of gefitinib rather than chemotherapy. BROWN *et al.* [53] conducted a study for the NICE. Patients were not selected for epidermal growth factor receptor (*EGFR*) mutations. Costs were considered too high for the British system, despite the fact that this was a selected population (IPASS (Iressa Pan-Asia Study Results) trial). NICE calculated the costs as ranging from £25 000 to £65 000 per additional QALY. The recently published study by DE LIMA LOPES *et al.* [54], adopting the perspective of Asian healthcare systems, analysed first-line gefitinib use in patients with *EGFR* mutations by comparison with chemotherapy. The results favoured gefitinib and this was confirmed by sensitivity analyses. The French ERMETIC (EGFR-Tyrosine Kinase Inhibitors in NSCLC) study found a cost/QALY ratio of €27 209 when treatment was guided by laboratory findings [56].

Costs of first-line tyrosine kinase inhibitor therapy are poorly documented.

Two recent papers focusing on elderly patients [57, 58] showed that although ratios remained high, at about €45 000 for dependent elderly patients and €30 000 for independent elderly

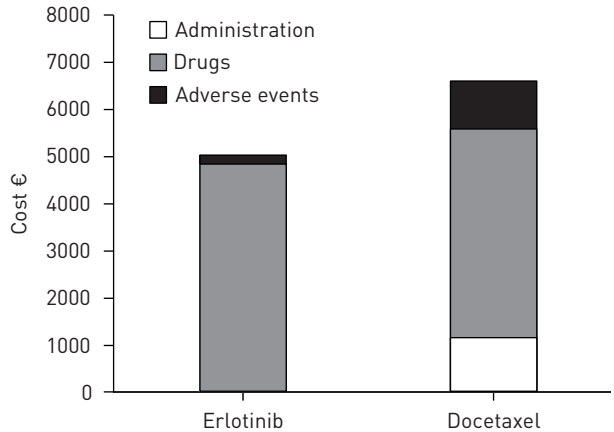

Figure 2. Cost distribution of products used for second-line treatment in 2009 euros. Reproduced from [49] with permission from the publisher.

patients, the use of erlotinib rather than chemotherapy did not increase costs and had no impact on the cost per QALY. Analyses based on clinical trials are even rarer. One such study [27], performed in China, calculated the cost of a year's treatment as US $11 556 (2010 dollars) for progression-free survival time and $14 519 for overall survival). A second study in Europe [59], based on a cost effectiveness analysis, showed that the erlotinib-first strategy was dominant in patients with *EGFR* mutations.

Antiangiogenic treatments

Antiangiogenic therapies have recently been used in patients with lung cancer but head-to-head comparisons with chemotherapy are rare [60]. Bevacizumab is the most extensively studied antiangiogenic drug, notably in the phase III trial by SANDLER *et al.* [61]. Published articles on the costs associated with this drug have been analysed in a general review [62].

Table 4. Economic analyses of gefitinib in NSCLC

First author [ref.]	Line	Type	Main results
CHOUAID [51]	Third	Modelling of a compassionate-use program French payer's perspective	Total costs: €39 979 ± 20 279 (10% of total costs)
HORGAN [52]	Second	Cost-utility analysis of INTEREST trial, gefitinib *versus* docetaxel	ICER CA $5161; gefitinib preferred
BROWN [53]	First	Modelling of first-line gefitinib *versus* chemotherapy	ICER £35 700 for gefitinib *versus* doublet therapy
DE LIMA LOPES [54]	First	Modelling of cost-effectiveness of EGFR TKIs *versus* standard care Asian payer's perspective	US $2400; dominant strategy

INTEREST: Iressa NSCLC Trial Evaluating Response and Survival against Taxotere; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; €: euro; ICER: incremental cost effectiveness ratio; CA $: Canadian dollar; £: pound sterling; US $: US dollar.

Among the five most interesting articles on the cost effectiveness of bevacizumab, two showed that it had acceptable cost effectiveness from the standpoint of German and Italian society [62, 63]. It must be stressed, however, that all these publications were model-based and did not use real clinical trial data.

Lung cancer screening

No study of lung cancer screening has been performed in Europe. MANSLEY and MCKENNA [65] envisaged nine different perspectives to evaluate screening. They showed that the choice of perspective had a marked impact on the findings and that the different points of view were quite divergent. The decision-maker's point of view had to take into account possible adverse effects and potential population-level consequences. The payer would have to assess the midterm economic consequences compared to initial costs. For their part, patients would seek immediate benefits.

In the study by MARSHALL *et al.* [65], screening of a high-risk cohort by spiral computed tomography (CT) would cost US $5940 per life-year saved. For the lowest-risk patients, screening still appeared cost effective (US $23 100 per life-year saved). MCMAHON *et al.* [66] conducted a medicoeconomic analysis of a randomised trial published by the National Lung Screening Trial Results in 2010. They used a model to compare CT screening, a smoking cessation programme and a combination of the two. Screening cost US $127 000–157 000 per QALY, which is much higher than for colon cancer or breast cancer in females ($32 000 and $47 000, respectively). Smoking cessation gave much lower costs (about $17 000 per QALY). However, a combination of the two approaches remained above $100 000 per QALY ($130 000–159 000). This model raised the difficult issue of unselected screening, which has not yet been validated at a medicoeconomic level. GOULART *et al.* [67] then evaluated the impact of a screening programme on healthcare spending in the USA. The assumption was that 10% of smokers between 55 and 74 years old could be covered by screening, representing approximately 3.5 million persons. If 75% of these persons were screened, it would entail an additional expenditure of about $2 billion. The cost per lung cancer death prevented would be $240 000.

Oxygen treatment

The cost of oxygen is rarely evaluated and most relevant studies are now very old. A French study estimated the cost of oxygen at 18 000 francs for 6 months of treatment [68].

More recently, the median costs for the first 2 months of oxygen delivery *via* an extractor were estimated at US $9703 for the extractor and $6515 for portable oxygen [69]. This result was highly dependent on care packages in the North American setting. The authors concluded that portable oxygen therapy did not result in additional costs and that it improved patients' quality of life. Prescription of home-based mechanical ventilation [70] was studied in the context of a clinical trial comparing the mechanical ventilation with oxygen therapy with home oxygen therapy alone. When the authors analysed the cost per patient in 2000 euros, there was a significant difference in favour of the combination of ventilation with oxygen.

In 2009, OBA [71] used a Markov model to assess the cost effectiveness of oxygen therapy in the long term, with a time horizon of 5 years. The model showed that oxygen prescription was cost effective, with a cost effectiveness ratio of US $16 124 per QALY, whereas purely nocturnal oxygen was not ($306 356 per QALY).

In 2011, VITACCA *et al.* [72] conducted a prospective 1-year cost analysis taking into account all medical consumption among patients treated with long-term mechanical ventilation or oxygen therapy. Three groups of patients were characterised: those treated with invasive mechanical ventilation, those treated with noninvasive mechanical ventilation and those treated with long-term oxygen therapy. The average annual cost was €21 926 per patient.

Conclusion

It is difficult to summarise in a single article the entire economic literature on respiratory diseases, and in this chapter we have focused on lung cancer and oxygen therapy. Cost effectiveness is clearly not the only criterion for judging a given therapeutic strategy or drug. However, economic studies are complementary to studies of quality of life, adverse effects and efficacy, and should be part of the clinical decision-making process as they reflect the impact of disease on society as a whole.

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Chapter 9

The economic burden of respiratory diseases: COPD and asthma

Rune Grønseth[1] and Sven-Arne Jansson[2,3]

The economic burden of COPD and asthma in Europe is substantial. According to the *European Lung White Book*, the annual cost per COPD case was approximately €2100 in 2011, whereas asthma costs were almost €3500 per case. Indirect costs accounted for 52% and 43% of COPD- and asthma-related costs, respectively. Recent studies were in line with these findings, but did indicate that previous estimates might be too conservative. For pneumonia, TB, interstitial lung diseases and pulmonary embolism there was scant information regarding population-based costs.

Similar to mortality and incidence, costs indicate the burden inflicted by a specific condition or disease on a society. In the field of respiratory medicine a large number of papers have attempted to quantify the economic burden of respiratory diseases. In this short chapter we have emphasised European population-based estimates of treatment-related costs and costs generated by productivity losses (short- and long-term absenteeism, as well as disability).

In order to critically appraise the literature, some basic concepts should be specified. By costs we mean the opportunity cost, *i.e.* what resources would have been made available if we chose to not spend them in the first place. These costs are seen from a given viewpoint or perspective, the costs of COPD for society at large differs from costs for a healthcare provider, a third-party payer and the patients themselves. Costs in the health economy are often classified as direct (treatment-related), indirect (related to diminished working capability, *i.e.* productivity losses) or intangible (*e.g.* emotional) costs. Cost studies that are incidence based present costs for the entire disease process, whereas prevalence-based studies most often present costs per year (irrespective of the stage of disease). Top-down studies identify diseased individuals after identifying cost-incurring events (*e.g.* from claims registers), whereas bottom-up studies first identify diseased individuals (*e.g.* by screening a population) and subsequently gather data concerning costs. In the latter studies, costs are often estimated by multiplying healthcare utilisation with unit costs. Each cost item is either attributed to a specific disease (attributable costs) or total costs are estimated and then compared with total costs in a control group (giving incremental or excessive costs) [1, 2].

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The *European Lung White Book* provides costs of respiratory diseases for European Union (EU) countries by combining published cost-of-illness studies with prevalence data, and adjusting them according to the gross domestic product per capita [3]. The authors estimate that respiratory illnesses account for direct costs of at least €55 billion and that the costs of lost production amount to at least €42 billion [3]. This chapter reviews the literature on population-based cost estimates in Europe for COPD and asthma, and provides brief reviews for pneumonia, TB, interstitial lung diseases (ILDs) and pulmonary embolism.

COPD

Being a chronic, progressive disease with an insidious onset, estimation of disease costs for COPD is not straightforward. There are some methodological issues that should be addressed. Undiagnosed COPD incurs a substantial burden to the healthcare system, and a large fraction of COPD patients remain undiagnosed or are misinterpreted as having asthma or other airway diseases [4]. Thus, prevalent cases should be detected or validated by post-bronchodilator spirometry, which should also be undertaken for cost-of-illness-studies [5]. There is also a large fraction of zero-utilisers among COPD patients [6], which are difficult to include in top-down studies. Exclusion of zero-utilisers inflates the costs per patient.

The authors of the *European Lung White Book* [3] assumed that undiagnosed individuals did not incur costs, which probably led to an underestimation of societal costs [4]. Bearing this in mind, they estimated that the annual direct costs per case in 2011 amounted to €1013 per case, whereas the indirect costs amounted to €1091 per case [3]. Total direct costs in the EU were estimated to be €23.3 billion and indirect costs €25.1 billion. At least four of the studies referred to in the *European Lung White Book* were not population based [7–10], and only two studies had identified cases by screening a general population by post-bronchodilator spirometry [11, 12]. Only one study estimated excessive costs, and this study did not verify diagnoses and included only hospitalisation costs and primary care visits [13].

Since 2011, five published studies have provided estimates of indirect or direct costs of COPD in European countries in population-based surveys (table 1) [11, 14–17]. Four of these identified cases by means of spirometry [11, 14, 16, 17], all of them applied the fixed ratio criterion ($FEV_1/FVC < 0.7$) and one study excluded subjects with $FEV_1 > 80\%$ of predicted values [17].

Three of the studies included control subjects and estimated excessive costs of COPD by FEV_1 in Norway [17], Germany [16] and Denmark [14]. Interestingly, the Norwegian and German excessive treatment-related costs of COPD with $FEV_1 < 80\%$ pred were quite similar, and even a bit lower than estimates given in the *European Lung White Book*, at roughly €900 per year [3]. The Danish study on excessive costs reported even lower costs for COPD irrespective of stage (€640, based on €1=DKK 7.46), which would be somewhat higher for $FEV_1 < 80\%$ pred [14]. The robust population-based methodology that these studies applied might be taken to indicate that the *European Lung White Book* did not provide conservative estimates [3]. The Norwegian study estimated that comorbidities and respiratory symptom exacerbations explain 37% of the excessive costs in COPD [17], in the German study almost 50% of excessive costs could be attributed to comorbidities in COPD with $FEV_1 < 80\%$ pred [16].

The obstructive lung diseases in Northern Sweden (OLIN) studies have published population-based cost-of-illness estimates using identical methodological for both 1999 and 2010 [11, 18]. In these studies there seemed to be a trend of declining costs for the most

Table 1. Population-based, European studies on the economic burden of COPD published since 2011

First author [ref.]	Study year, Country	Population	COPD criterion, control group	Design	Costs included	Results	Comments
Jensen [14]	2004, Denmark	General population, aged ⩾45 years	COPD: post-bronchodilator FEV_1/FVC <0.7 (n=546) Controls: all other (n=3995)	Bottom-up, retrospective (1 year) Prevalence based Incremental costs, human capital approach Unclear cost perspective	Direct and indirect costs (includes transfer payments)	Total excessive public healthcare costs DKK 4779 per year, 60% inpatient care, remainder mainly drug costs. Social benefits (excessive) DKK 15 901 per year	Unclear methodology No unit costs listed Very low response rates Does not discriminate between costs and transfers
Jakobsen [15]	2010, Denmark	General population, aged ⩾40 years	COPD: combination of drug use in ATC R03 and hospitalisation with a COPD diagnosis (n=166 462)	Top-down, prospective, but retrospective identification Prevalence based Attributable costs Societal perspective	Drug costs (third-party payer and co-payments)	Average COPD drug cost (ATC R03) was DKK 7842, estimated lifetime costs DKK 70 000–75 000	Diagnoses are unverified Ignores non-utilisation
Menn [16]	2009, Germany	General population, aged ⩾40 years	COPD: pre-bronchodilator FEV_1/FVC <0.7 (n=375) Controls: all other (n=1880)	Bottom-up, retrospective One interview (12 months): self-reported utilisation Societal treatment-related costs Prevalence based Excessive costs	Outpatient services Inpatient services Drugs	No excessive costs in GOLD spirometric stage I COPD, €990 for stage II COPD and above Adjustment for comorbidities: reduces excessive costs by almost 50% in stage II COPD and above	Pre-bronchodilator COPD definition Recall bias
Nielsen [17]	2005, Norway	General population aged ⩾40 years, ever-smokers Comparison with hospital-recruited COPD patients	COPD: post-bronchodilator FEV_1/FVC <0.7, FEV_1 <80% pred (population-based COPD n=81; hospital-recruited COPD n=205) Controls: post-bronchodilator FEV_1/FVC >0.7, FEV_1 >80% pred (n=132)	Bottom-up, prospective Prevalence based Four telephone interviews in 1 year: self-reported utilisation Societal perspective, treatment-related costs Excessive costs	Direct costs: hospitalisation, healthcare visits, drugs, oxygen treatment, nursing services, rehabilitation	Median annual, population-based excessive treatment-related costs €918 Costs in hospital-recruited patients: €3340 Higher costs with more severe disease Adjustment for comorbidities and exacerbations: €81 per symptom-defined exacerbation, €461 per comorbid condition	Only ever-smokers No patients with FEV_1 >80% pred Low number of severely affected population-derived patients
Jansson [11]	2010, Sweden	General population, aged 39–84 years	COPD: post-bronchodilator FEV_1/FVC <0.7 (n=244)	Bottom-up, prospective (one interview every third month) Prevalence based Attributable costs Societal Human capital approach	Direct costs: physician visits, hospitalisation, oxygen therapy, drugs Indirect costs: sick leave and early retirement due to respiratory diseases	Mean direct costs for GOLD stage I–IV COPD were €269, €1029, €2201 and €5351, respectively Mean indirect costs were €327, €2216, €3485 and €12 004, respectively	Low number of severely affected patients

ATC: Anatomical Therapeutic Chemical Classification; DKK: Danish kroner; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

severely ill, but this finding was not statistically significant. However, drug costs and outpatient costs increased significantly for those with moderate and mild spirometric obstruction, respectively [11].

When it comes to analysis of indirect costs, several studies add to the estimates provided by the *European Lung White Book*: the OLIN studies [11, 18] and the Danish excessive costs paper [14]. The latter provided an estimate of excessive costs of €2749 per year. However, this included costs that were classified as transfer payments, and thus did not represent costs to the society, merely transactions between individuals. JANSSON *et al.* [11] estimated indirect costs due to sick leave and early retirement (table 1) and showed that for all disease stages indirect costs outnumbered the direct costs, and that this difference increased almost exponentially with increasing severity. Both studies adopted the human capital approach, assuming that all sick leave and disability represents a cost for society to the same degree. This assumption can be challenged, but to our knowledge, no study within the field of respiratory medicine has presented population-based, indirect costs using a friction-based approach [1].

To summarise, the indirect and direct costs of COPD are related to disease severity as measured by FEV1. The indirect costs are at least as large as the direct costs, and a large fraction of the costs seems to be related to comorbidities and exacerbations. The *European Lung White Book* estimates [3] might be too conservative when they emphasise costs of diagnosed individuals, and are only partially built on population-based studies with high external validity. There is an obvious need of more studies based on case-finding with high-quality screening of general populations, particularly with regards to indirect costs.

Asthma

Asthma is a major health problem in society. Studies about costs of asthma have been performed in many countries, both in Europe and in other parts of the world. Most of the cost-of-illness studies have derived their estimates from official statistics (top-down approach) [19] or from clinically selected samples [20]. However, there is a lack of studies where the data has been collected at the subject level (bottom-up approach) [19] from representative samples of asthmatics from the general population [21, 22].

The *European Lung White Book* estimated costs for asthma for the EU countries [3]. As for COPD, estimates of direct costs presented by disease severity were modelled using linear regression analysis, adjusted for severity and the setting from which the patients were recruited [3]. The severity of asthma was graded according to the Global Initiative for Asthma classification. The annual direct costs per case in 2011 were estimated to amount to €1950 per case, while the indirect costs amounted to €1450 per case [3]. Total direct costs in the EU were estimated to be €19.5 billion and indirect costs to be €14.4 billion. At least seven of the papers referred to in the *European Lung White Book* were not population-based studies [23–29], and only two studies were based on the general population [21, 22]. None of the studies estimated excessive costs, and only one study estimated costs for exacerbations [28].

During 2013 and 2014, four published studies have given estimates of direct or indirect costs of asthma in the European countries (table 2) [30–33]. One observational, cross-sectional, multicentre study in a sample of 1100 asthmatics from Spain was mainly focused on indirect costs (both absenteeism and presenteeism) [30]. They also estimated direct costs; however, costs for drugs were not included. They found that the direct costs due to healthcare use for a 3-month period were significantly higher in older patients (€2104 in patients aged

Table 2. European studies on the economic burden of asthma published since 2011

First author [ref.]	Study year, country	Population	Design	Costs included	Results
Ojeda [30]	2010, Spain	Asthmatics from outpatient clinics, aged 18–65 years	Cross-sectional, observational, epidemiological multicentre study	Direct (except drugs) and indirect costs	Direct costs for healthcare consumption and indirect costs were higher in older patients Costs increased with disease severity Lack of disease control yielded higher costs compared with controlled asthma
De Miguel-Díez [31]	2002–2010, Spain	Children (age 0–15 years) and young adults (age 16–45 years) hospitalised for asthma exacerbations	Register-based, retrospective, descriptive epidemiological study	Costs for hospital admissions for asthma exacerbations	Direct costs decreased from 2002 to 2010 in the group of paediatric patients By contrast, the direct costs increased in young adults
O'Neill [32]	2012, UK	Patients with SRA Comparison with a group with difficult-to-manage, but non-SRA disease	Patient-specific anonymised healthcare data drawn from the BTS National Registry for dedicated UK Difficult Asthma Services	Direct healthcare costs	Annual mean treatment costs for SRA patients were £2912 to £4217 These costs are higher than those for patients with poorly controlled ''difficult asthma''
Doz [33]	2010, France and Spain	Asthma patients recruited by GPs, aged ⩾18 years with a diagnosis of asthma for at least 12 months	Observational study in primary care Patients recruited during a 1-year period, retrospective data collection (the 3-month period before inclusion)	Direct and indirect costs (sick leave)	The average total cost of controlled asthma was €342 per patient in France compared with €1256 for partially controlled asthma and €2152 for uncontrolled asthma In Spain, the corresponding figures were €610, €965 and €2227

SRA: severe refractory asthma; GP: general practitioner; BTS: British Thoracic Society.

18–40 years *versus* €3302 in patients aged 41–65 years). The direct costs also increased progressively with the level of asthma severity (€520 in patients with mild intermittent asthma *versus* €699 in patients with severe persistent asthma). The same trend was found for disease control, with lack of disease control yielding the highest costs. A similar pattern was found for the indirect costs [30].

One study estimated the changes in incidence, use of mechanical ventilation, length of stay, costs and mortality from 2002 to 2010 among children (age 0–15 years) and young adults (age 16–45 years) hospitalised for asthma exacerbations [31]. They found a decrease in the incidence of hospital admissions for asthma exacerbations with a concomitant increase in use of noninvasive ventilation in both paediatric and young adult asthmatic patients. The mean direct cost decreased from €1558 in 2002 to €1378 in 2010 in the group of paediatric patients. By contrast, the mean cost per patient increased from €2183 in 2002 to €2564 in 2010 in young adults.

The study by O'Neill *et al.* [32] estimated the direct healthcare costs of treating severe refractory asthma and analysed which factors were most important in driving costs in the UK. Annual mean treatment costs among severe refractory asthma patients were £2912 to £4217 per subject per year. Significant predictors of costs were FEV_1 % pred, location of care, maintenance oral corticosteroid treatment and BMI.

In an observational cost-of-illness study conducted simultaneously in France and Spain for all types of costs, with asthma patients recruited prospectively by general practitioners in 2010, the percentage of patients using healthcare resources varied significantly according to the level of asthma control [33]. The average cost of controlled asthma was €342 per patient in France compared with €1256 for partially controlled asthma and €2152 for uncontrolled asthma. In Spain, the corresponding figures were €610, €965 and €2227 [33].

Based on the prevalence of asthma in the different EU countries, the referred studies published during 2013 and 2014 correspond to a large extent with the total costs presented in the *European Lung White Book* [3]. However, the total costs could be somewhat underestimated.

In conclusion, both direct and indirect costs are strongly correlated to severity of asthma and increasing age. Furthermore, there is need for more research especially bottom-up studies, which show to a greater extent the true costs in the general population compared with top-down studies based on selected samples from primary care or hospital based cohorts.

Pneumonia

As with COPD, there are distinct features of pneumonia that deserve attention when estimating costs. First of all, to diagnose pneumonia an infiltrate on chest radiography is needed. But in everyday medical practice, pneumonia is often a clinical diagnosis based on signs of systemic infection with involvement of the lower airways. The latter is often classified as ALRI. Furthermore, it might be difficult to decide when an episode of pneumonia starts and when it ends, and how to attribute resource use to a specific episode. Finally, to gather data regarding pneumonia in a population-based sample would require a significant effort from participants, as well as all levels of healthcare providers.

The *European Lung White Book* [3] identified two studies presenting costs of pneumonia in Europe [34, 35]. The study by Bauer *et al.* [35] exclusively presented hospitalisation costs,

whereas BARTOLOMÉ *et al.* [34] presented both outpatient and inpatient costs. Based on these two papers, pneumonia is associated with a total inpatient cost of €2.5 billion per year. Neither study estimated indirect costs.

We have not been able to find any new European, population-based estimates of pneumonia costs published since 2011. Several papers have been published based on large claims-databases in the USA, but none with clinically confirmed pneumonia.

Tuberculosis

Valid and representative data regarding aggregated total costs for TB in the individual EU member countries are sparse. The main reasons are a lack of health economic studies estimating the magnitude of the costs for TB. Furthermore, the incidence varies considerably between different European countries and the costs differ substantially between the different countries.

The *European Lung White Book* tried to summarise the costs for TB for EU countries [3]. Estimates of costs related to TB are based on the recent review by DIEL *et al.* [36] for 27 EU countries (excluding Croatia), quoted as 2012 values. This analysis includes estimation of the direct healthcare costs associated with multidrug-resistant (MDR)- and extensively drug-resistant (XDR)-TB. The *European Lung White Book* estimated that the annual total costs per case in 2011 amounted to €7467 per case (fully sensitive TB €6832; MDR-TB €33 320 and XDR-TB €47 573). Total costs in the EU were estimated to be €0.54 billion. However, due to the known differences in incidence and costs between the EU countries, the estimated costs could be regarded as quite uncertain [3].

The course of TB tends to be short-lived, with total treatment and costs concentrated within the year of diagnosis. The direct costs of cases of drug-resistant TB are considerably higher than those associated with drug-sensitive disease. Consequently, because of the nature of the disease, in most patients the estimates for TB approach the lifetime costs, but they represent only a small proportion of lifetime costs for asthma and COPD.

Interstitial lung diseases and pulmonary embolism

There is a remarkable paucity of literature on costs of ILD and pulmonary embolism. However, the first entity represents a complex group of low prevalence diseases for which it might be difficult to recruit a sufficiently powered study, and the second represents a disease that often remains undiagnosed. Reviewing the literature published after 2011 we found one paper providing direct costs for idiopathic pulmonary fibrosis based on a US claims-database of subjects older than 55 years of age [37]. For pulmonary embolism we found several papers based on claims-analyses in the USA [38, 39], and one German paper presenting claims-based cost-analyses from 2000–2006 [40]. The latter estimated that direct costs (outpatient physician, medication, impatient care, nursing care and other) were €5815 and €8960 more for males and females, respectively, that survived the first year after pulmonary embolism, compared with matched controls surviving admissions due to other causes [40].

Conclusion

Population-based estimates of the economic burden associated with specific lung diseases provide decision-makers with information with external validity. For both COPD and asthma

there is relatively comprehensive literature, presenting both indirect and direct costs. However, there is a clear need for population-based cost-of-illness studies of pneumonia, TB, interstitial lung diseases and pulmonary embolism.

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Chapter 10

Sex, gender and respiratory health

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Research on the relationships between sex and gender and respiratory health suggests an impact on incidence, susceptibility and life-course pattern for respiratory diseases. This chapter reviews evidence of the impact of sex and gender on smoking, lung cancer, COPD and asthma, and outlines the possible mechanisms underlying gender differences.

Worldwide, reductions in age-standardised daily smoking rates have been reported since 1980 from 41.2% to 31.1% for men, and from 10.6% to 6.2% for women. Gender differences in smoking affect the rates of lung cancer and COPD, which are on the increase worldwide, varying considerably across regions and countries. Sex ratios of asthma rates are more homogenous (around 1.2 to 1.5), but exhibit a characteristic lifetime pattern.

Considerable gender differences are reported for smoking, lung cancer, COPD and asthma. To improve the quality and effectiveness of healthcare by gender sensitive approaches, we need unbiased comparisons of men and women and insights into the mechanisms involved in producing sex and gender differences.

Sex and gender differences in respiratory health have increasingly been explored in the last few decades. 10 years have passed since the comprehensive *Monograph* was edited by S. Buist and C.E. Mapp, broadly addressing sex- and gender-related differences in airway anatomy, airway physiology and immunity over the lifespan of a human, and focusing on gender differences in different domains of respiratory medicine [1]. In 2007, a comprehensive review on gender differences in asthma development and progression covered literature from 1980 to 2007 [2]. The role of sex and gender for respiratory conditions has been explicitly addressed [3–16] and chapters on respiratory health were included in three recent gender medicine textbooks [17–19]. This body of research accumulates evidence that suggests an impact of sex and gender on incidence, susceptibility and life-course pattern for several respiratory diseases.

It is of public health and medical relevance to explore this area; the integration of sex and gender aspects is crucial to cope with morbidity and mortality of respiratory diseases, which are expected to increase worldwide [20]. There is also a practical and clinical endeavour. In order to improve healthcare, in terms of quality and effectiveness, by being gender sensitive we need unbiased comparisons of men and women, insights into the mechanisms involved in

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producing sex and gender differences, including sociocultural aspects in medical research and care, and possibly gender-sensitive clinical guidelines [17].

To evaluate the role of sex and gender as a risk factor or as a determinant of respiratory diseases, we need to go beyond simple comparisons between men and women or boys and girls. To understand the observed differences, we need to know which mechanisms are involved in producing these differences. In addition, conceptualisations of sex and gender have considerably evolved over time [21–26]. From being virtually absent in the 1970s, the notion of "gender" has increasingly found a place in medical literature, as a distinct construct to "sex", or interchangeably used with "sex", taking over new meanings and mirroring changing beliefs and theoretical approaches [21] and resulting in an inconsistent use in medical journals [22]. The early focus on women had been expanded to include both, women's and men's perspectives [27–31]. Furthermore, methodological issues regarding gender analyses and the integration of gender analyses into basic and applied sciences have become a topic (http://genderedinnovations.stanford.edu/) [26, 31–33].

Currently, a distinction between sex and gender is maintained: sex denotes genetic and biological characteristics and gender refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviours and values that society ascribes to the sexes on a differential basis [21]. Some attempts explicitly aim at clarifying the use of these terms in biomedical research by underscoring the importance to explicitly define and accurately use them (http://genderedinnovations.stanford.edu/) [32]. However, a clear-cut distinction of sex and gender has been questioned again [22–26]. The use of the term sex as a "stand-alone indicator of biology" [26] is rejected given that gendered experiences materialise in the body and measures of sex include effects of gender. Despite the acknowledgement that sexed biological bodily processes interact with surrounding gendered social and cultural events from birth throughout life [22], the interactions between sex and gender are far from being completely understood.

This chapter builds on previous work on the relationship between sex and gender and respiratory diseases. Mechanisms, through which sex and gender impact on respiratory diseases (*e.g.* through gendered exposures) are outlined and recent research is reviewed with a focus on sex and gender differences in smoking, lung cancer, COPD and asthma.

Mechanisms/pathways involved in sex and gender differences

As for other chronic diseases, a considerable number of sex- and gender-related paths can produce differences in respiratory diseases (fig. 1).

Genetic mechanisms maybe involved, such as gene polymorphisms involved in metabolising tobacco-associated carcinogens or influencing DNA repair, leading to risk modification of lung cancer [34]. Oestrogen receptor-α gene variants may play a role for a differential development of bronchial reactivity in men and women [2]. Further gene variants may be underlying the heritability of asthma [35].

Gender differences arise due to differences in physiology or anatomy, in terms of body size, lung size and airway diameter. Girls, on average, have smaller lungs and fewer respiratory bronchioles at birth and female neonates tend to have higher corrected flow-rates compared to male neonates, suggesting that the ratio of their large to small airways is higher [2]. The

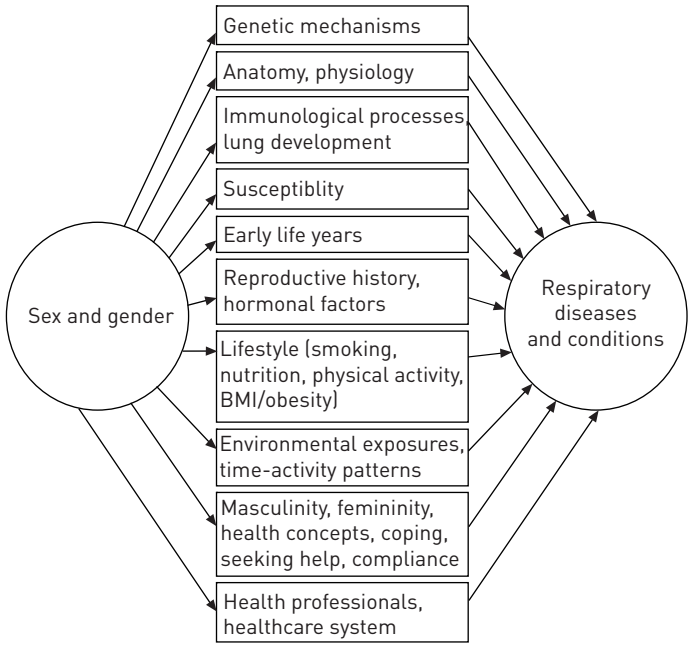

Figure 1. Sex- and gender-related pathways producing gender differences in respiratory diseases and conditions.

increased risk for asthma and bronchial hyperreactivity in women in early adulthood seems partly explained by their smaller airway calibre [13, 36, 37].

Lung development is achieved through a complex process including organogenesis, fetal development, post-natal development and immunological processes. Maturation appears to be more advanced in female than in male fetuses [2]. Developmental processes continue during childhood and adolescence, playing a role for the higher asthma incidence in boys compared to girls, and possibly for the higher asthma prevalence in women in adulthood [3, 4].

Differential susceptibility to the effects of substances such as smoke, smoke carcinogens and further environmental exposures presents another pathway producing gender differences in respiratory health [8, 38, 39], and may contribute to the explanation for the higher incidence of cancer in female smokers [35]. Susceptibility may also be relevant for test settings that involve substances, such as those used in airway-reactivity testing [37].

Factors present early in life affect health later in life [40]. These involve intrauterine programming as well as postnatal conditions. A role has been shown for nutritional factors *in utero*, breastfeeding, or disadvantageous factors in the first years of life [40–43].

Reproductive life history and hormonal factors have been suggested to affect, in particular, asthma, based on a characteristic life-time pattern of asthma [3]. Research also showed hormonal influences for lung growth, airway calibre and lung size [10] and associations between indicators of hormonal disbalances, such as menstrual irregularities or the polycystic ovarian syndrome with a number of respiratory conditions [16, 44–46].

Gendered lifestyles lead to differential consequences for respiratory health in men and women. This is most prominent for smoking [47], but is also observed for nutrition, and

further behavioural differences and also for differences in time-activity patterns, which in turn entail different environmental exposures; indoor as well as outdoor, occupational as well as traffic-related [48].

The way in which a subject incorporates health and disease into the personal and social identity is interrelated with meanings of masculinity and femininity [27–29, 49]. These sociocultural processes impact on many stages of respiratory conditions: health concepts, symptom presentation, seeking help, coping with disease, and compliance [36, 50]. It was impressively shown for the way in which teenage boys and girls "managed" asthma and diabetes [49]; the majority of girls showed greater adaptation incorporating their conditions and their treatment regimens into their social and personal identities, whereas boys made every effort to keep asthma and diabetes out of their personal and social identities. These conditions were not seen as a threat by girls but they were by boys.

It has also been shown that health professionals and the health system are responding to men and women in different ways, impacting on diagnostic reasoning [6, 51] and diagnostic and treatment procedures [36, 52].

It is crucial to consider which pathways are relevant, given their very differing implications. Gender sensitive considerations may have to deal with many aspects, ranging from physiologic features, as in test settings (dose considerations), to targeting recommendations for health behaviour, preventing exposures or rising awareness of gendered ways for coping with one's health, gendered reactions and interpretations, and of gendered diagnostic and treatment decisions from health professionals.

Sex and gender as determinants of respiratory conditions

The role of sex and gender have been addressed for a large variety of respiratory conditions, both for common diseases such as asthma, COPD or lung cancer, as well as for more rare disorders, such as pulmonary hypertension [53], cystic fibrosis [54–56] or interstitial lung disease [35, 57]. This chapter is not comprehensive but focuses on the most common conditions.

Smoking

Worldwide, smoking rates for men are approximately five times higher than those for women, but there is a wide variation in gender differences across regions and countries (table 1) [58, 59]. While gender differences are largest in China, with a smoking prevalence of 53% in men compared to 2% in women [47], they are considerably smaller in other regions. The ratio of female-to-male smoking prevalence is greater than one in Sweden [60], where smoking rates for men are at 13% and those for women are at 15%. Recent survey data in adolescents aged 13–15 years suggests a closing of the gender gap in smoking in the youth [59, 61]. In many countries, the tobacco epidemic followed a similar pattern, in which smoking first increased among men and then among women as a result of changing social and cultural norms. Women were, and in some geographical areas still are, better protected against tobacco use, which is strongly rooted in prevailing norm for masculinity and contradicting norm for femininity [62]. Greater autonomy and changes in women's roles were associated with smoking uptake in Western countries, prompting predictions of similar patterns in developing countries [62]. However, these cultural norms have undergone changes in Western countries, having led to equal ranking of smoke-related risks for men and women [59]. Smoking rates for men have declined in the second half of the 20th century,

Table 1. Sex and gender as determinants of smoking prevalence

Smoking prevalence	[Ref.]	Men %	Women %	Male/female unadjusted ratio
Worldwide 2010	[58]	36	7	5.14
China 2010	[47]	53	2	26.5
USA 2012	[59]	24.8	19.3	1.28
Europe 2006	[47]	22	17	1.29
Sweden 2012	[60]	12.8	15.1	0.85

followed by a parallel decline in adult women since the 1980s in Western countries [47]. Worldwide, large reductions have been observed for age-standardised prevalence of daily tobacco smoking between 1980 and 2012, with reductions from 41.2% to 31.1% in men and from 10.6% to 6.2% in women [63]. Due to population growth, the number of smokers remains on the increase [63]. Smoking is increasingly concentrated among those with low socioeconomic status [47]. Large disparities in tobacco use persist between ethnic populations, among groups defined by educational level, socioeconomic status, geographic region, degree of religiosity, sexual minorities (including individuals who are gay, lesbian, bisexual and transgender, and individuals with same-sex relationships or attraction) and severe mental illness [59, 64, 65].

Smoking has to be seen as the single most important health hazard, based on its' prevalence, particularly for men [59]. The effectiveness of tobacco interventions for smoking cessation developed specifically to meet needs of women and men have recently been reviewed [66, 67]. While only very few studies targeted men, there was a larger number of interventions targeting women. While they produced similar abstinence rates as non-sex-/gender-specific programmes, they particularly attract women who may otherwise not seek any treatment [67].

Lung cancer

Considerable variations of lung cancer incidence rates are documented across regions and countries, with consistently higher rates in men than women [7, 68]. The highest incidence rates were observed in Northern America (table 2), where lung cancer is now the second most frequent cancer in women, and in Central and Eastern Europe. Within the European region, sex ratios of lung cancer incidence are highest in Central and Eastern Europe (5.9) and lowest in Northern Europe (1.8). Lung cancer mortality shows a similar geographic pattern as incidence [68], with a worldwide mortality rate 2.5 times higher in men than in women, and the highest sex ratios found in Central and Eastern Europe. In many of the more developed countries the incidence in men has reached a plateau, or is decreasing, whereas in women it continues to increase, reflecting prior and long-term exposure in particular to tobacco smoke. The majority of lung cancer deaths is now occurring in developing countries.

Phenotypic and histologic differences in lung cancer are known between men and women. Peripheral lung adenocarcinomas are more common in women than in men, in contrast to squamous cell carcinomas, which are more common in men [11, 69, 70]. Smoking appears to be the most dominant risk factor for men and women [34, 71]. Different smoking patterns have been reported in women and men [35], with a lower amount of tobacco consumption in women with lung cancer than in men with lung cancer [72, 73]. Also, the risk of developing lung cancer without any smoking history is higher in women [69, 74]. The risk of lung cancer

Table 2. Sex and gender as determinants of lung cancer

Lung cancer	Men	Women	Male/female unadjusted ratio
Incidence			
Worldwide 2008	34.0	13.5	2.5
More developed countries	47.4	18.6	2.5
Less developed countries	27.8	11.1	2.5
Northern America	48.5	35.8	1.4
Northern Europe	39.3	21.9	1.8
Western Europe	44.7	16.7	2.7
Southern Europe	49.0	10.4	4.7
Central and Eastern Europe	57.0	9.6	5.9
Mortality			
Worldwide 2008	29.4	11.0	2.7
More developed countries	39.4	13.6	2.9
Less developed countries	24.6	9.7	2.5
Northern America	37.9	24.7	1.5
Northern Europe	32.2	18.8	1.7
Western Europe	37.1	12.9	2.9
Southern Europe	42.3	8.5	5.0
Central and Eastern Europe	51.6	7.9	6.5

Data for men and women presented as n cases per 100 000 population (age-standardised). Data taken from [68].

increases with decreasing lung function in men and women, being amplified in women [11]. A higher susceptibility of women to carcinogens of smoke is discussed for these gender differences based on genetic reasons [11, 35]. Capacity for DNA repair is lower in women, and there are gender differences in smoke metabolism [75, 76]. Environmental tobacco-smoke exposure is associated with an excess risk for lung cancer of 20% to 40% [77]. For women exposed to smoking spouses, consistent findings of an increased lung cancer risk have been reported in a number of meta-analyses across continents, and no important heterogeneity was observed between results of cohort and case–control studies [77]. Women's risk for lung cancer has furthermore been related to exposures associated with fossil fuel burning for cooking in particular in developing countries, or cooking vapours released from the oil used in cooking [7]. While the vast majority of studies on occupation and lung cancer were conducted in men, recent studies in women from the USA, Europe and China report similar or higher risks [34].

COPD

For methodological reasons, comparisons regarding COPD were long and complicated. Efforts made to standardise prevalence estimates now enables us to account for differences in definitions and severity [20, 78–80]. Even with identical methodologies, prevalence rates based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of COPD show a considerable variation across countries (table 3); higher rates are reported for men when compared with women in the majority of countries (table 3) [79–87]. In some countries prevalence rates are higher in women, such as in the USA and Australia, and no gender differences are observed in others, such as Austria or Iceland [87]. Within Canada, age and sex differences have been shown to account for most of the heterogeneity in COPD

estimates across five sites [15]. Only a few studies are providing COPD-incidence rates separately for women and men, reporting adjusted hazard ratios for men in the range of 1.8 to 2 [83–85]. According to DE MARCO *et al.* [88], sex and age distribution varies considerably depending on the used diagnostic criteria, with incidence rates being higher in men when using the GOLD definition, but lower when relying on lower-limit of normal definitions. COPD mortality rates of men currently exceed those of women [86]. COPD continues to be an important cause of mortality, and this is expected to increase particularly in low- and middle-income countries [11, 20]. An increasing trend is also expected for COPD prevalence, more pronounced in women, due predominantly to population ageing and smoking trends.

Smoking has been well established as a dominant cause of COPD [20] both for men and women, and the variations in COPD prevalence and mortality may reflect, as is the case for lung cancer, historical trends in smoking. However, it has been recently recognised, that a considerable proportion of COPD cases cannot be explained by smoking alone or by a misclassification of asthma as COPD [89]. An estimated 24–45% of subjects with COPD have never smoked and the burden of nonsmoking COPD is expected to be higher than previously believed. The relevance of other causes of COPD has been underestimated [5, 88, 89, 90]. A particular role for women is discussed for obesity, systemic inflammation, reproductive factors and exposure to environmental tobacco-smoke and air pollution [8, 33].

Research points to a differential susceptibility for men and women to tobacco-smoke and environmental exposures [9, 11, 79, 91–94]. This is supported by a meta-analysis of longitudinal studies showing a faster annual lung function decline in female, compared to male, smokers [8], and pulmonary function improving more with smoking cessation in women than in men [95]. It is still debated whether these findings are due to: a differential susceptibility on the background of genetic predisposition; smaller airway sizes in women, which lead to a proportionately greater exposure [37, 92]; or whether susceptibility is

Table 3. Sex and gender as determinants of COPD

COPD	[Ref.]	Men	Women	Male/female ratio
Prevalence %				
GOLD stage II in population-based studies	[20]	9.8	5.6	1.75#
GOLD stage II by age in Netherlands	[81]			
40–49 years		13.3	8.0	1.7#
50–59 years		13.7	8.2	1.7#
60–69 years		18.9	6.9	2.7#
⩾70		19.9	15.6	1.3#
Overall		4.4	1.2	3.7#
Range of prevalence	[82]	2.9–41	2.4–34.2	
Incidence n (95% CI)				
Norway aged 18–74 years	[83]	8.6 (5.1–12.0)¶	3.6 (1.3–6.0)¶	2.0 (0.9–4.3)+
Netherlands aged >40 years	[84]	3.54 (3.3–3.8)¶	2.3 (2.2–2.5)¶	1.65 (1.49–1.82)+
Netherlands aged 55–90 years	[85]	14.4 (13.0–16.0)¶	6.2 (5.5–7.0)¶	1.8 (1.41–2.19)+
Mortality				
Range of annual COPD rates in 2007	[86]	12.5–49§	2.7–23.7§	

GOLD: Global Initiative for Chronic Obstructive Lung Disease. #: unadjusted ratio; ¶: cases per 1000 person-years; +: adjusted hazard ratio (95% CI); §: rates per 100 000 population.

amplified by further factors such as body weight, physical activity, systemic inflammation and reproductive factors [8, 9, 93]. The increase in COPD prevalence observed particularly in women may not only be due to an increase in tobacco and occupational exposure among women, but also to differences in the susceptibility to exposures. Gender differences have been described for how professionals diagnose and treat COPD patients [35]. Diagnostic reasoning of primary care physicians was shown to differ by patient gender in studies conducted in Canada and Spain [51, 96], with COPD being more likely to be underdiagnosed in women. Further reasons underlying gender differences in COPD are related to comorbidity [35]. Women with COPD appear to be more affected by depression and psychological distress and perceive worse control of their symptoms [35, 97].

Asthma

While the sex ratios for asthma prevalence and incidence vary less than for lung cancer and COPD, this disease exhibits a characteristic life-course pattern that differs for men and women. Lower rates of prevalence and incidence are consistently observed in girls in comparison to boys, up to adolescence, in many countries, whereas in adulthood the rates are reported to be higher in women than in men (table 4). In most studies, approximately two-thirds of children with asthma or wheezing are boys and one-third are girls [36, 102]. The shift towards higher rates occurs around the age of 15 years [36, 98]. This pattern is similar for prevalence rates from cross-sectional studies and for data from case–control studies, birth cohorts and twin registers [12]. For incidence in childhood, the magnitude of male/female ratio is around 1.3–1.5 [12]. In adulthood, asthma prevalence is reported to be 1.2–1.5 times more frequent in women than in men [99, 100]. There are only a few studies reporting sex-specific incidence rates for adults, also showing higher asthma incidence rates in women [99, 101, 103]. For "methodologically best" studies EAGAN *et al.* [101] reported an incidence rate of 4.2 (95% CI 2.4–7.4) per 1000 person-years for men and 4.9 (95% CI 3.0–8.0) per 1000 person-years for women, which yielded a female/male ratio of 1.2. It seems that the sex-rate ratio decreases with increasing age, but there is a lack of knowledge particularly for the elderly. There are also open questions regarding the observed sex- and age-related age course pattern according to atopic and nonatopic asthma. LEYNAERT *et al.* [99] reported asthma incidence to increase with age only among nonatopic women. A trend towards higher estimates of adult incidence in more recent studies has been described, and a parallel increase in estimates of adult asthma incidence for both sexes between the 1960s and 1990s [101]. For studies with age-adjusted risk estimates, the increased risk with greater age was most pronounced in the highest age group [101].

A range of pathways seem to produce gender differences in asthma. Due to gene variants, heritability of asthma seems to be especially pronounced in male offspring [35]. Some polymorphisms are particularly related to asthma in females [104]. The female sex predicts persistence of asthma from childhood to adulthood [105]. Developmental factors play a role for the higher asthma rates in boys; whereas the large airways tend to grow faster than parenchymal tissue in girls, the growth of large airways tends to lag behind that of the parenchyma in boys, resulting in relatively narrower airways in young males than in females [10]. Differential maturation occurs furthermore in adolescence and young adulthood, with lung growth continuing longer in males than females, leading again to a difference in the relationship between airway diameters and lung volumes [106].

The relationship of asthma to atopy seems to differ in males and females; girls have been reported to suffer from more frequent associations of asthma with allergic rhinitis and atopic

Table 4. Sex and gender as determinants for asthma

Asthma	[Ref.]	Men	Women	Male/female unadjusted ratio
Prevalence %				
Children/adolescents				
UK aged 1–5 years	[12]	12.7	9.2	1.4
Netherlands aged 11 years	[98]	7.7	7.4	1
Netherlands aged 16 years	[98]	4.3	6.2	0.7
Adults				
ECRHS II by age	[99]			
28–35 years		6.6	6.3	0.95 (0.66–1.37)[f]
36–44 years		5.74	6.85	1.21 (0.91–1.60)[f]
45–52 years		4.69	7.52	1.68 (1.24–2.29)[f]
USA	[100]	7.2	9.7	1.35
Incidence of new asthma or wheeze				
Children/adolescents[#]				
UK by age	[12]			
0–7 years		2.9	2.3	1.23
8–11 years		1.3	1.0	1.3
12–16 years		0.85	0.58	1.47
17–23 years		0.56	0.94	0.59
Canada by age[¶]	[12]			0.53
12–24 years		2.8 (1.7–3.9)	5.3 (3.6–7.0)	
Adults				
EAGAN by age[+]	[101]			
35–36 years		2.3	4.7	2.0
50–51 years		3.2	5.0	1.56
65–66 years		4.9	3.9	0.8
60–69 years		3	8	2.7
⩾70 years		2	6	3
ECRHS by age[§]	[101]			
20–27 years (at baseline)		2.3 (1.3–3.4)	3.7 (2.5–4.98)	1.58 (0.91–2.75)[##]
28–35 years		1.6 (0.8–2.2)	4.4 (3.2–5.6)	2.76 (1.6–4.77)[##]
⩾36		2.98 (2.1–3.8)	4.1 (3.2–5.2)	1.40 (0.96–2.04)[##]

Data are presented as follows: [#]: % per year; [¶]: 2-year cumulative incidence median (range) %; [+]: cases per 1000 person-years; [§]: cases per 100 person-years (95% CI); [f]: OR (95% CI); [##]: hazard ratio (95% CI). ECRHS: European Community Respiratory Health Survey.

dermatitis. However, allergy to grass and dust mites has been more frequently associated with asthma in boys [35] and male sex is associated with higher IgE concentrations in children [2]. In adults, differences in asthma incidence have been shown to be limited to nonatopic asthma [99]. A higher BHR in women has been reported, which was explained by airway size in some but not all studies, and the role of airway size remains controversial [13, 37, 107].

Based on the lifetime pattern, reproductive and hormonal factors have been suggested to play an important role in asthma [3, 16, 44, 108]. Reproductive life history and hormonal factors have been shown to impact a number of respiratory conditions [16, 44–46], in particular influencing lung growth, airway calibre, and lung size [10]. A role for hormones is also suggested by research, showing changes of asthma and bronchial reactivity across the menstrual cycle [109] and in pregnancy [108]. Sex hormone levels may also vary according to metabolic situations, such as polycystic ovarian syndrome (a metabolic syndrome), obesity, or physical activity, which are all related in addition to respiratory conditions [44, 110]. The

role of obesity for asthma seems to be higher in women than in men, in particular for nonallergic asthma [111, 112]. The underlying mechanisms are not yet fully understood, but an interaction with hormonal factors has been discussed [44, 108].

Seeking help and responses from health professionals are also involved in gender differences found with asthma. Although female asthma patients seem to suffer from more symptoms than males, males are more likely to be diagnosed with the disease [113]. Women are reported to have a higher frequency of routine asthma visits and higher hospitalisation rates [35]. However, several studies have shown an under-diagnosis and an under-treatment of asthma in girls when compared with boys and in adolescent women [52, 113–115]. Also, gender differences in prescriptions of specific medications have been described [35].

Conclusion

The higher smoking prevalence of men translates into a higher burden for lung cancer and COPD in men, but it is on the increase in women. Smoking prevention appears of paramount importance, particularly in developing countries and low socio economic populations to counter balance unfavourable trends. Cessation interventions targeting men and women with gender-sensitive approaches might reach women otherwise not seeking treatment. Gender differences in smoking affect the rates of lung cancer and COPD, varying considerably across regions and countries. Sex ratios for asthma are less variable but show a characteristic pattern across life, with a shift from higher rates in boys compared to girls to higher rates in women compared to men.

Sex and gender sensitive research is needed because sex and gender rank among the key factors that determine respiratory health, alongside socioeconomic status, ethnicity, and age, and is more likely to lead to improved outcomes in treatment and preventive interventions. Sex and gender affect biological vulnerability, development, exposure to health risks, experiences of disease and disability, access to medical care and public health services and responses of the health system. It is crucial to consider which pathways are relevant given their very differing implications.

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Disclosures: None declared.

Chapter 11

Genetic factors in asthma and COPD

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In the past few decades, identification of genes predisposing to development of asthma or COPD has been the focus of many candidate-gene studies and genome-wide association studies. Acknowledging the role of environmental factors like cigarette smoking, air pollution and job-related exposures, current studies focus on identification of genetically susceptible groups for these specific exposures. Gene-by-environment interaction studies (candidate gene-by-exposure interaction studies, genome-wide interaction studies and epigenetic studies) aim to identify genetic loci that predispose to asthma and COPD onset after exposure to such environmental risk factors. This chapter gives an overview of the current knowledge of genetic risk factors and gene–environment interactions underlying asthma and COPD.

Asthma and COPD are both diseases that run in families. The heritability estimates for asthma range from 40% to 60% [1]. COPD heritability is estimated to be 37% [2]. Both asthma and COPD are complex disorders with heterogeneous phenotypes, and are probably caused by a complex interaction between genetic make-up and the environment.

The systematic genetic studies on respiratory diseases started about half a century ago with family-based linkage studies. These studies identified linkage to asthma [3] and COPD [4–6] in several genetic loci. With the increase in technical genotyping possibilities and the completion of the Human Genome Project in 2003, the number of genetic studies on asthma and COPD has increased exponentially. Current genetic association study approaches can be broadly categorised as candidate-gene studies and genome-wide association (GWA) studies. A candidate-gene study focuses on a gene or several genes with a known function that may be relevant to a disease. It is a hypothesis-driven approach. Conversely, a GWA study is a hypothesis-free approach, and tests the association between hundreds of thousands of single-nucleotide polymorphisms (SNPs) and the disease of interest. The SNPs are chosen in such a way that the whole human genome is represented. Both approaches have methodological advantages and disadvantages. For example, the candidate-gene study is capable of identifying associations with SNPs with low allele frequency. In a GWA study, these so-called rare variants are usually not included in commercial arrays or are excluded from the analysis after genotyping as, due to the mandatory multiple testing correction, the statistical power of a GWA study is too low. However, the GWA study can identify unexpected SNPs for the disease of interest, which may open new avenues of research and understanding of the pathophysiology of the disease.

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A very important point in genetic studies is the definition of the phenotype to be investigated. For asthma, the phenotype of interest is very often self-reported, doctor-diagnosed asthma and no clinical testing is performed. This may lead to a bias in the estimated asthma prevalence but may also result in not identifying genetic associations due to this "poor" phenotyping. Using measurable clinical parameters of asthma may overcome this problem. This approach thus focuses on subphenotypes or combinations of subphenotypes assumed to be important in asthma, such as BHR, lung function or atopy. The definition of COPD is usually based on lung function. The Global Initiative for Chronic Obstructive Lung Disease criteria use a fixed ratio of $FEV_1/FVC < 70\%$, but in recent decades, studies have shown that this underestimates the prevalence of COPD in younger subjects and overestimates COPD prevalence in the elderly [7]. This problem can be tackled by using the so-called lower limit of normal, which takes the age of the subject into account, to define COPD [8].

A problem with GWA studies is that many subjects have to be investigated as many statistical tests are performed and, thus, multiple testing correction is needed. It is practically impossible for one study centre to recruit enough subjects to perform a well-powered GWA study. Therefore, researchers collaborate and consortia are formed. In these consortia, great care should be taken that all centres have the same definition of cases and controls or use exactly the same continuous trait, such as lung function. Moreover, potential confounders may differ between the consortium members due to cultural and social differences. Another problem is that the associations found in the identification cohorts should be replicated in other cohorts, again with the same definition of the phenotype to be investigated. These replication cohorts are not always available.

The genetic contribution to asthma and COPD is very complex, and interactions between different genes or between genes and the environment complicate these studies even further. Humans do not all live in the same environment and, therefore, the association between genes and health outcomes might be largely driven by the environment. For example, a gene that regulates processes involved in the handling of cigarette smoke will only be important if the individual is exposed to cigarette smoke. When no cigarette smoke is present in the environment, the effect of the gene is probably not seen [9–11]. This makes the research into genetics of asthma and COPD even more complex. The number of studies incorporating gene–environment interactions is increasing. For candidate-gene studies, it is not difficult to do this in a methodologically sound manner but for GWA studies, the best statistical and methodological approaches are still under debate [12].

Candidate-gene studies in asthma

Many candidate-gene studies have been performed in asthma comparing cases and controls. The most often replicated genes are *TNF* (encoding TNF-α), *IL4* (IL-4), *FCER1B* (FcεRIβ), *ADAM33* (encoding an "a metallopeptidase and disintegrin" domain-containing protein), *GSTP1* (glutathione *S*-transferase π1), *ORMDL3* (encoding an orthologue of the *Saccharomyces cerevisiae* ORM1 protein), and *IL13* (IL-13) (fig. 1), and these studies have been reviewed extensively [13, 14]. In addition to these case–control studies, studies on the association between candidate genes and a phenotype within asthmatics only (case-only design) can be performed. The study by IERODIAKONOU *et al.* [15], in which SNPs in *TGFB1* (transforming growth factor-β_1) were found to be associated with asthma severity, airway inflammation and remodelling in a consistent manner, is a good illustration of this. One has to bear in mind that genes associated with the development of asthma do not necessarily have to be associated with the severity of asthma as well and *vice versa*. In fact, studying the

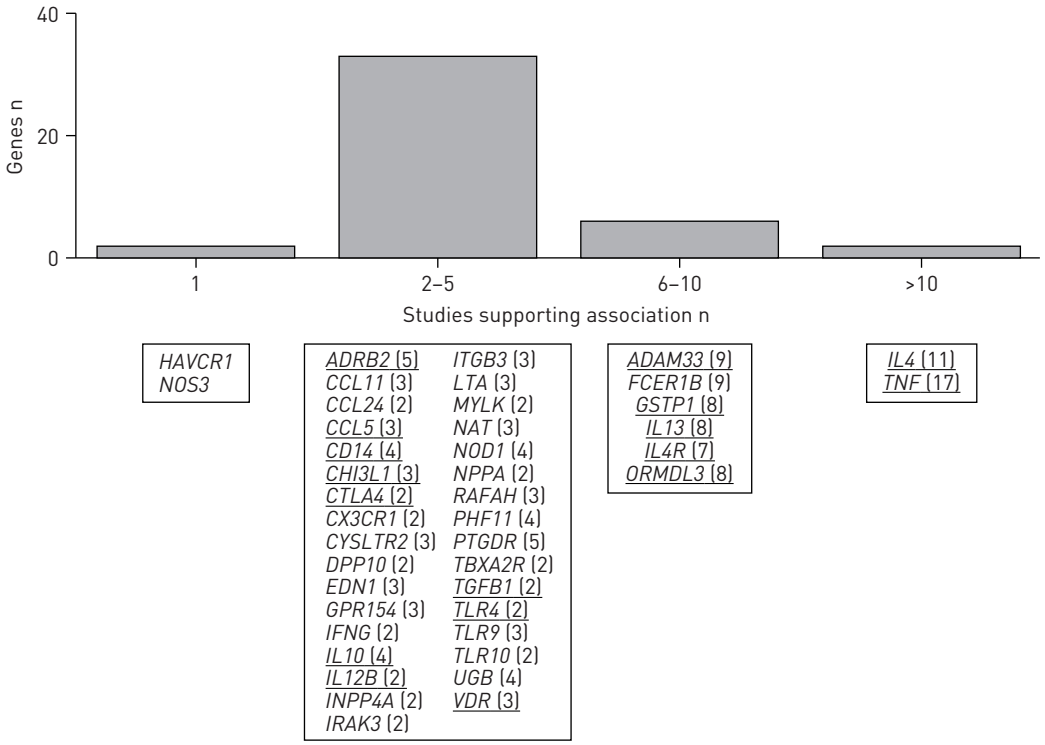

Figure 1. Candidate genes that have been associated with asthma in at least one study of samples greater than a total of 300 subjects (150 cases and 150 controls) and have been replicated in at least one other population with the same single-nucleotide polymorphism. The upper part shows a histogram of the number of asthma susceptibility genes based on the number of publications supporting a significant genetic association. The lower part shows the corresponding genes in each bar. Official gene symbols are used. The number of publications that are supportive is indicated in parentheses. Underlined genes are associated with both asthma and COPD. Reproduced and modified from [13] with permission from the publisher.

genetics underlying asthma onset and asthma severity are two different research questions, and thus different candidate genes can be hypothesised. Other candidate genes that have been found to be associated with a phenotype among asthmatics are, for example: *IL6R* (IL-6 receptor) with lung function [16]; *ADAM33* and its flanking genes with lung function and exacerbation rates [17], and with lung function decline [18]; *SERPINE1* (plasminogen activator inhibitor) with asthma severity [19]; arginase genes (*ARG1* and *ARG2*) with asthma severity [20]; *PLAUR* (plasminogen activator, urokinase receptor) with lung function decline [21]; *ESR1* (oestrogen receptor 1) with BHR and lung function decline [22]; *CDH1* (E-cadherin) with lung function decline, inflammation and remodelling [23]; and *TPSAB1* (α-tryptase) with IgE and lung function [24].

GWA studies in asthma

The three main GWA studies on asthma have been performed within the GABRIEL consortium [25], the EVE consortium [26] and the Analysis in Population-based Cohorts of Asthma Traits (APCAT) study [27]. In these consortia, the associations between genes and asthma were analysed separately for the different cohorts, and the results were meta-analysed. GABRIEL identified the following genes to be associated with asthma in subjects of European

descent: *IL18R1* (IL-18 receptor 1) (*IL1RL1*; IL-1 receptor-like 1), *HLA-DQ* (a class II human leukocyte antigen), *IL33* (IL-33), *SMAD3*, *ORMDL3/GSDMB* (gasdermin B)/*GSDMA* (gasdermin A), *IL2RB* (IL-2 receptor β), *TSLP* (thymic stromal lymphopoietin; only in severe asthma), *SLC22A5* (the high-affinity sodium-dependent carnitine cotransporter), *IL13* and *RORA* (RAR-related orphan receptor A) [25]. The EVE study included asthmatics with other ethnicities (European American, African American, Afro-Caribbean and Latino), and their results show associations between SNPs in *IL1RL1*, *TSLP*, *IL33* and *GSDMB* and asthma in all ethnic groups. In addition, they identified the *PYHIN1* gene (interferon-inducible protein 10) to be associated with asthma only in individuals of African descent [26]. The APCAT study identified, in addition to the previously identified genes, a locus in the *HLA* region as being associated with asthma in subjects of European descent [27]. Interestingly, none of the genes associated with asthma in the candidate-gene studies was identified in the GWA studies, indicating that both study designs have their own merit and should be performed in parallel.

GWA studies in asthma subphenotypes

As asthma has a very heterogeneous phenotype, attempts have been made to perform GWA studies on subphenotypes in asthma. For example, the association between *ORMDL3* and asthma seems to be present only in childhood-onset asthma [28]. In the recent study by Ferreira *et al.* [29], a GWA study on asthma with hay fever, the same genetic variants as in the abovementioned asthma GWA studies (GABRIEL, EVE, and APCAT) were found but, in addition, two other SNPs (in *ZBTB10* (encoding a zinc finger- and BTB domain-containing protein) and in *CLEC16A* (a C-type lectin)) reached genome-wide significance. Likewise, a GWA study on asthma with recurrent severe exacerbations found an additional association with a variant in *CDHR3* (encoding a cadherin-like protein) [30]. Many other disease characteristics may be important in the identification of genes that are only modestly associated with asthma in general but may be very strongly associated with a subphenotype of asthma based on these characteristics. Possible disease or patient characteristics to be included are age of onset, BHR, atopy, lung function, reversibility, age, sex and ethnicity. The recent application of latent class analysis to identify wheezing phenotypes [31] may be a very useful tool to use in genetic studies on asthma. The study by Siroux *et al.* [32] nicely applied this approach and found different SNPs to be associated with different asthma phenotypes. The SNPs identified in previous asthma GWA studies were replicated in at least one of the phenotypes (mostly with their "active allergic asthma" phenotype). Unfortunately, as the number of subjects per subphenotype is, by definition, smaller than the total number of subjects with asthma, the statistical power to detect an association is reduced in this subphenotype analysis. A solution to this would be either to recruit even larger sample sizes or to make the significance thresholds used in GWA studies less stringent in order to prevent prematurely discarding potentially important associations.

The GWA study design has also been applied in case-only approaches in which the association between genes and a phenotype is analysed within asthmatics only. Although the number of subjects in these analyses is relatively small, the advantage of this is that a continuous outcome parameter can be used, which increases the statistical power. Examples of this approach are the studies in asthmatics on the severity of BHR [33] or on the level of lung function [34]. As expected, the identified SNPs in these studies are not the same as in the case–control GWA studies of asthma, as the research question and the outcome studied are very different.

Gene-by-environment interaction studies in asthma

Candidate gene–environment interactions in asthma

The genetic studies of asthma only explain a small part of the heritability. This suggests that other factors might play a role as well. A very obvious risk factor is the environment. Some candidate-gene studies have been performed investigating gene–environment interactions. The predominant environmental exposures studied are air pollution and environmental tobacco smoke (ETS). The recently published TAG (Traffic, Asthma and Genetics) study found that the risk of asthma in association with nitrogen dioxide exposure was only increased in children carrying at least one minor allele of SNPs in the *GSTP1* gene and not in the homozygous major allele carriers [35]. An overview of asthma studies investigating gene-by-air pollution interactions was given by VAWDA *et al.* [36]. That review showed that the association between air pollution exposure and respiratory function is modified by genes controlling innate immune recognition of foreign material (*TLR4*; encoding Toll-like receptor 4) and the subsequent inflammatory response (*TGFB1* and *TLR4*). An example of a study on gene-by-ETS smoke exposure interaction is the study by WANG *et al.* [37] in which the greatest risk of asthma was found in children with more ETS exposure and at least one minor allele of the C160A polymorphism in the *CDH1* gene. Another good illustration of a candidate gene–environment interaction is the interaction between exposure to farming or farm milk consumption in early childhood and the *CD14* innate immunity gene. In these studies, the protective effect of exposure to farming or farm milk consumption on the development of asthma or allergy is dependent on the *CD14* genotype [38, 39].

Genome-wide interaction with environment in asthma

Gene–environment interactions can also be included in a GWA study, in a so-called genome-wide interaction (GWI) study. EGE *et al.* [40] performed both a candidate gene-by-environment interaction study and a GWI study with exposure to farming as the environmental factor. They concluded that only relatively rare SNPs, and not the more common genetic variants, moderate the protective effect of exposure to farming on asthma and allergy. SCHOLTENS *et al.* [41] performed a GWI study for the GABRIEL consortium investigating interactions between SNPs and *in utero* and early-life tobacco smoke exposure in the development of asthma before the age of 16 years. Some suggestive evidence for an interaction between *in utero* tobacco smoke exposure and a SNP in *EPB41L3* (encoding an erythrocyte membrane protein band 4.1-like protein), and for an interaction between early-life tobacco smoke exposure and a SNP in *PACRG* (a parkin-coregulated gene) was observed. In the previously mentioned APCAT study [27], a search for interactions between genes and smoking or allergic status (in this case, hay fever) was also performed. Some SNPs interacting with either smoking or allergic status were identified but unfortunately these did not reach genome-wide significance (p-values for the top interacting SNP were 8.6×10^{-6} and 2.3×10^{-6}, respectively). Therefore, these interacting SNPs were not further analysed. This nicely illustrates that the statistical power problems of GWA studies become even larger in a GWI study, as analyses of interaction have a lower study power than analyses of main effects.

Candidate-gene studies in COPD

COPD is characterised by chronic airway obstruction, and permanent and progressive respiratory symptoms like cough and breathlessness. COPD is a major cause of death

throughout the world and its prevalence is still increasing [42, 43]. As smoking is considered the main risk factor for COPD but not all smokers develop COPD, genetic susceptibility to the deleterious effects of smoking has been primary focus in genetic studies of COPD. Subsequently, the first candidate-gene studies on COPD focused on genes that plausibly played a role tissue damage and repair (*e.g.* proteases and antiproteases), oxidative stress (oxidant–antioxidant balance), and inflammatory pathways due to inhalation of noxious particles. Genes involved in the regulation of oxidative stress in the lung, such as *HMOX1* (haem oxygenase 1), *NFE2L2* (NEF2-related factor), superoxide dismutase genes and *GCLC* (encoding the catalytic subunit of glutamate–cysteine ligase) [44–47], indeed confirmed that some people are genetically susceptible to smoking, but a number of susceptibility genes for COPD beyond smoking have been shown to be important too, like *ADAM33*, *TIMP1* (tissue inhibitor of metalloproteinases 1) and *MMP12* (matrix metalloproteinase 12) [48–50]. Apart from a large amount of case–control studies of the genetics of COPD, a number of studies of accelerated lung function decline, which is often considered a key feature in COPD development, identified *MMP1* (matrix metalloproteinase 1), *GSTP1*, *GSTT1* (glutathione *S*-transferase τ1), *GSTM1* (glutathione *S*-transferase μ1), *HMOX1* and *SERPINA1* (α_1-antitrypsin) as being related to the onset of COPD or accelerated lung function decline [51, 52].

A meta-analysis of candidate genes previously associated with COPD, using strict criteria for inclusion of studies, showed that three *TGFB1* polymorphisms, and *IL1RN* (IL-1 receptor antagonist) variable number tandem repeat polymorphism increased the risk of COPD. The *TNF* -308 G/A polymorphism was related to an increased risk of COPD and the *GSTP1* I105V polymorphism was associated with a decreased risk of COPD in the Asian populations only, showing the importance of ethnicity in identifying specific COPD genes [51, 52]. Another meta-analysis identified the same but also other genes to be important in COPD onset, namely *GSTM1*, *TGFB1*, *TNF*, *SOD3* (superoxide dismutase 3), *IL1RN* VNTR, *GSTP1*, *EPHX1* (epoxide hydrolase 1), *ADRB2* (β_2-adrenoreceptor), *CHRNA5* (nicotinic acetylcholine receptor (nAChR) α_5-subunit), *CSF3* (granulocyte colony-stimulating factor), *IL1RN*/*IL1B* (IL-1β), *IL4R* (IL-4 receptor), *IL6* (IL-6), *IL8* (IL-8), *IL10* (IL-10), *IFNG* (interferon-γ) and *ADAM33* [52, 53].

In the most recent review updating the evidence for genes related to COPD, an extensive list of the COPD-associated genes was published [54]. The number of publications supporting the evidence for genes associated with COPD or related phenotypes are shown in figure 2.

GWA studies in COPD

The two first GWA studies on COPD identified variants in the nAChR subunit genes, such as *CHRNA3/5* and *CHRNB3/4* [9, 55, 56]. These variants had been shown to be associated cross-sectionally with nicotine dependency and smoking status, as well as with the level of lung function and COPD (defined by airway obstruction) and lung cancer [9, 55–57]. Since the gene is associated with the presence and severity of emphysema as well, independent of pack-years of smoking exposure, this suggested that the nAChR cluster is causally involved in alveolar destruction as a potentially shared pathogenic mechanism in lung cancer and COPD. However, because this gene is also associated with nicotine addiction and smoking is the main risk factor for COPD development, the issue whether the nAChR variants determine COPD development directly or indirectly *via* smoking addiction was debated [9]. The only longitudinal analyses investigating whether SNPs in the nAChR cluster are associated with smoking habits and lung function decline, and whether these potential associations are independent of each other, showed that SNPs in the nAChR region were associated with

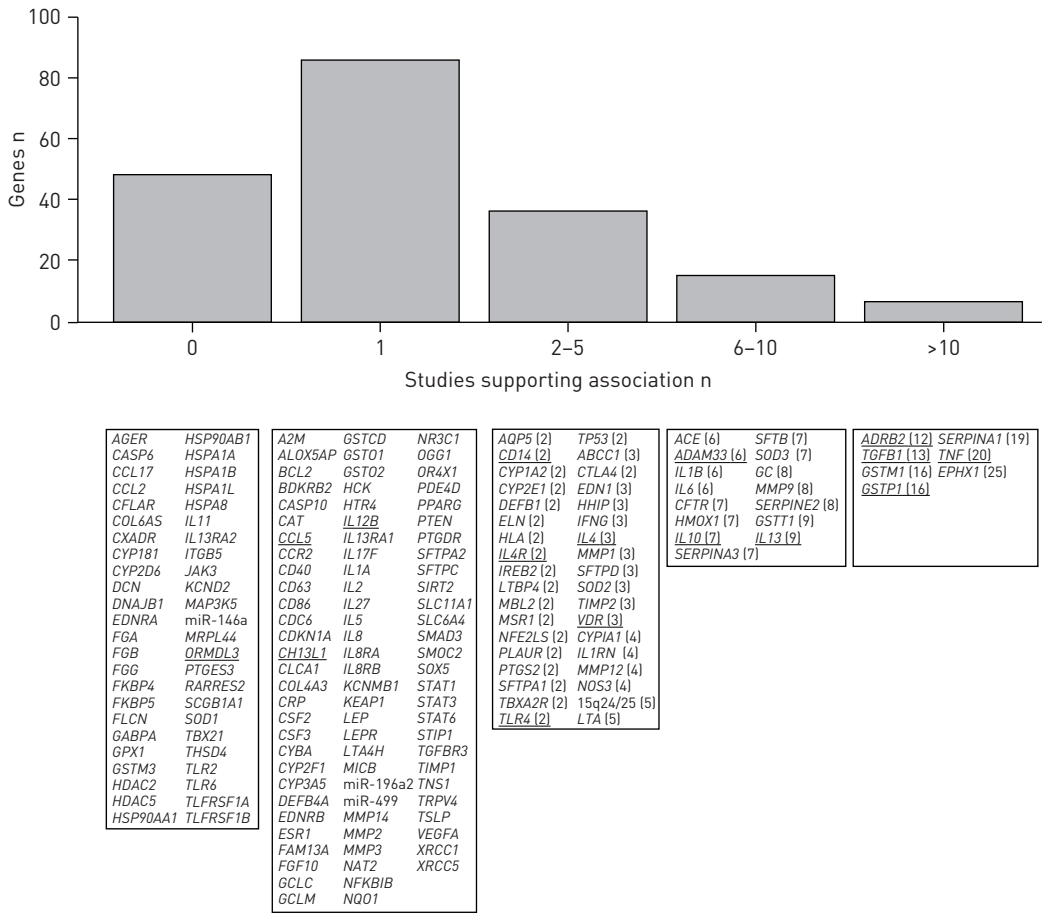

Figure 2. Candidate genes associated with COPD or related phenotypes. The upper part shows a histogram of the number of COPD susceptibility genes based on the number of publications supporting a significant genetic association. The lower part shows the corresponding genes in each bar. Official gene symbols are used. The number of publications that are supportive is indicated in parentheses. Underlined genes are associated with both asthma and COPD. Reproduced from [54] with permission from the publisher.

smoking habits such as quitting smoking, but had no significant effect on the annual FEV_1 decline in smokers and ex-smokers. This suggests a potential role of these SNPs in COPD development *via* smoking habits rather than direct effects on lung function [58]. These findings should be replicated in larger longitudinal cohort studies.

GWA studies in COPD subphenotypes

It is now widely acknowledged that COPD is a heterogeneous disease. Some patients with COPD may have predominantly emphysema, others expressing airway disease or any combination of the two. Different subphenotypes in COPD will likely have different genetics underlying the difference in expression (*e.g.* genes associated with airway obstruction, commonly used to define COPD in epidemiological studies, are probably different from those determining emphysema or small airway disease). Thus, GWA studies only analysing lung function as a COPD phenotype will not dissect the full spectrum of disease and many genes will go undetected that are relevant to emphysema or small airway disease.

The first GWA study looking at the percentage of emphysema using computed tomography identified regions in or near *SNRPF* (small nuclear ribonucleoprotein polypeptide F) and *PPT2* (palmitoyl-protein thioesterase 2) [59]. The genetic variants in these genes were previously implicated as genes influencing lung function and analyses including lung function revealed independent associations for percent emphysema in Caucasians, additionally showing that genes related to α-mannosidase may influence risk of emphysema. Moreover, specific analyses among Hispanic and Chinese subjects identified a genetic locus for upper-lower lobe ratio near the α-mannosidase-related gene *MAN2B1,* and among Chinese subjects, loci near *DHX15* (RNA helicase 2) and *MGAT5B* (mannosyl-(α-1,6)-glycoprotein β-1,6-*N*-acetylglucosaminyltransferase isozyme B), which acts on α-linked mannose. The ethnicity-related findings observed earlier in relation to airway obstruction thus also seem to hold for emphysema [51].

GWI with environment in COPD

Since the genetic epidemiological research field has been dominated by a smoking-related focus on the origins of COPD, until recently, unexplained COPD development in nonsmokers has been ignored. As it is estimated that as much as 25–45% of COPD patients have never smoked [60], clearly, other factors, both environmental and genetic, contribute to the development of COPD. However, until recently, GWA studies aiming to find novel susceptibility genes associated with COPD have disregarded environmental factors that may underlie the development of this disease.

GWI with active cigarette smoking

Not surprisingly, active tobacco smoking was the first environmental risk factor that was studied in relation to genome-wide susceptibility to COPD, in a GWI study. HANCOCK *et al.* [61] were one of the first to performed such a study, showing that genome-wide gene–environment interaction studies, in their case with personal smoking (ever smoking or pack-years of exposure), yield novel loci associated with the level of lung function (FEV_1 and FEV_1/FVC) that would be missed when only focusing on direct genetic effects. It is of course likely that individual genetic susceptibility is important for occupational exposures, air pollution exposures and ETS exposure too.

GWI with job-related exposures

So far, only one GWI study on job-related exposures of lung function using a community-based population has been published [62]. The SNP-level analysis suggests that a SNP in gene *SLC38A8* (encoding a putative sodium-coupled neutral amino acid transporter) may significantly modify the effect of occupational exposure on FEV_1. The results of network analysis suggest that *HDAC* (histone deacetylase), *PPARA* (peroxisome proliferator-activator receptor α) and *CTLA4* (cytotoxic T-lymphocyte-associated protein 4) play important roles in the gene-by-occupational exposure interaction network. Unfortunately, given the total lack of replication in comparable cohorts, this study does not meet current state-of-the-art standards and, therefore, its results should be interpreted with caution. Other GWI studies with appropriate replication are currently ongoing or in press, among which is a study investigating several types of occupational exposures, *i.e.* biological dust, mineral dust, and gases and fumes, using standardised methodology, such as a job–exposure matrix, specifically designed for population-based studies (*e.g.* the ALOA+JEM) [63].

GWI with air pollution

As several studies have shown that there are direct acute health effects of increasing air pollution levels in susceptible groups [64] and differences in response to air pollution between adult males and females [65], air pollution might be one of the exposures leading to COPD in genetically susceptible subjects. GWI studies with air pollution trying to identify genes that give an increased risk of developing COPD are currently underway and might unravel yet unexplained non-smoking-related COPD onset in the general population.

GWI with other environmental exposures

There are strong suggestions that (poor) dietary habits also may affect subjects with specific genetic variants. For example, for every level of vitamin C intake, lung function was worse if smokers had an SNP in the *GCLC* gene, a detoxification gene associated with COPD in two cohorts [45]. Therefore, GWI with dietary factors in relation to COPD onset should be explored in the near future too. In general, GWI studies will lead to identification of genetic loci that might lead to altered gene expression levels, changed protein structures, altered microRNA (miRNA) levels or DNA methylation upon exposure. Determining the functional mechanisms of the identified genetic variants will be an important focus in future studies.

Post-GWA and post-GWI studies on asthma and COPD

In forthcoming years, research will focus on genome-wide gene–environment interaction studies of asthma and COPD, and several novel loci will be identified. An important future challenge of these studies will be to understand the functional consequences of these loci, for example, whether a SNP changes protein structure or gene expression. Going from an identified and replicated SNP to a functional meaning of this newly identified variant is important to unravel fully the pathways underlying the development of asthma and COPD. This knowledge also enables the translation of the findings into clinical benefits, such as biomarkers, drug targets, screening and prevention strategies [66]. There are several ways to proceed from identified SNPs to functional mechanisms. The most obvious option is to perform functional or experimental studies in the laboratory using a variety of methods including assays and cell cultures, as well as gene knock-out models in animals. A good illustration of these functional laboratory studies is a study of serum urokinase receptor (uPAR) levels, which is involved in obstructive lung disease, that identified human plasma kallikrein as a post-translational regulator of uPAR levels [67].

Other options include various "omics" approaches such as transcriptomics, metabolomics or epigenomics. For example, mRNA expression analysis assesses whether a SNP is associated with expression of a gene nearby (*cis* expression quantitative trait locus (eQTL)) or further away (*trans*-eQTL). SNPs can also be associated with metabolite levels (mQTL) that may be an intermediate phenotype between genetic variation and disease. Studying genetic regulation of both gene expression and biochemical conversions (metabolites) may help to uncover how genetic variation affects disease susceptibility and progression [68].

In addition, comparison of gene expression and metabolic profiles of patients and healthy controls may lead to new biomarkers for screening or specific disease phenotypes for more tailored therapeutic interventions. An attempt to use metabolite profiles for diagnosis and monitoring of respiratory diseases has led to the development of so-called electronic noses that assess metabolic compounds in exhaled breath condensate [69].

Other options for post-GWA study analysis include resequencing and epigenetic ("above" genetic) mechanisms. Resequencing or fine mapping may be used to capture the causal SNP that is correlated with the SNP associated with the outcome under study (linkage disequilibrium). In addition, fine mapping or deep sequencing in genetically isolated populations or as a complementary approach to GWA studies may also be used to identify rare variants associated with asthma or COPD, thereby potentially explaining some of the "missing heritability" of the disease. The importance of these rare variants was nicely illustrated by a recent reanalysis of the GABRIEL study on asthma [70]. In this reanalysis, the SNPs with a minor allele frequency lower than 1% were also included and the results show that 45% of the 109 SNPs with a p-value $<7.2\times10^{-8}$ are rare variants. Epigenetic mechanisms, such as DNA methylation, histone modification and miRNAs, contribute to gene regulation, and may mediate associations between SNPs and disease found in GWA or GWI studies [66, 71]. An important focus of future studies will be on the role of these epigenetic mechanisms in both asthma and COPD. As epigenetic alterations are believed to be induced by environmental exposures, they are considered to be a plausible path by which exposures can lead to the development of complex airway diseases [72, 73]. The most commonly studied epigenetic process is DNA methylation. Genome-wide methylation patterns were shown to be associated with prenatal tobacco smoke exposure [74, 75], smoking status and time since quitting [76–78], air pollution exposure [79, 80], as well as with the presence and severity of asthma [81] and COPD [82]. As platforms for high-throughput DNA methylation analysis are increasingly available and costs are decreasing, this seems to be a promising methodology to study the effects of exposure in epidemiological research. We envision these studies will improve our comprehension of how genes and the environment can lead to asthma and COPD onset in the general population.

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Chapter 12

Early life events including transgenerational epigenetic effects on respiratory outcomes

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Many children suffer chronic respiratory morbidity with troublesome symptoms and lung function abnormalities persisting into adulthood. There are many early life events that increase the risk of this adverse outcome. These include intrauterine growth retardation, antenatal smoking and premature delivery, particularly if the infant then develops bronchopulmonary dysplasia. Respiratory viral infections in infancy are associated with increased wheeze and asthma at follow-up, although some children may have a genetic and/or a functional predisposition to developing a symptomatic LRTI. Further longitudinal studies are required to better understand how early life events may regulate transgenerational epigenetic effects and lead to asthma.

Many children suffer chronic respiratory morbidity, including recurrent troublesome respiratory symptoms and asthma requiring prolonged treatment that may persist into adulthood. These adverse outcomes are common in infants born very prematurely, particularly among those who developed bronchopulmonary dysplasia (BPD). Although their lung function improves with increasing age, the most severely affected remain symptomatic in adolescence and young adulthood with lung function abnormalities indicating airflow limitation. Prematurity, sadly, is only one of a number of early life events that adversely affect long-term respiratory outcome. This chapter reviews the most common events (table 1), identifies possible mechanisms of these adverse respiratory outcomes and explores whether transgenerational epigenetic effects are an important link between early life events and adult disease.

Prematurity

Very premature birth with or without BPD development is associated with significant respiratory morbidity during infancy. Among 492 infants born prior to 29 weeks gestation, at both 6 and 12 months 27% were coughing and 20% wheezing, 14% were receiving bronchodilators and 8% inhaled steroids [1]. Prematurely born children with BPD, however,

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Table 1. Common early life events contributing to chronic respiratory morbidity in childhood and beyond

Premature birth with and without the development of bronchopulmonary dysplasia [1, 2]
Intrauterine growth retardation [3, 4]
Maternal smoking during pregnancy [5, 6]
Mode of delivery [7, 8]
Post-natal respiratory viral infections [9, 10]

had greater morbidity at follow-up than those who did not develop BPD. In a cohort study at 7–8 years of age, 24% of children born prematurely and 30% of those who had BPD were wheezing compared with only 7% of term controls [2]. In young adulthood, those who had BPD reported significantly more respiratory symptoms compared with those who were born prematurely but did not develop BPD and term controls [11]. The BPD subjects had more wheezing, episodes of pneumonia, exercise limitation and use of long-term medication than those in the other two groups ($p=0.047$ and $p=0.0001$, respectively) [11].

Rehospitalisation was more common in prematurely born children, in particular those who had BPD, than in children born at term. Respiratory viral infections, in particular RSV, are the most common cause of readmission in infancy [12]. Even in young adulthood (18–27 years) among 4674 adults who were very low birth weight and low birth weight infants, the risk of respiratory hospitalisation was increased; compared with 18 445 term controls, the odds ratios were 1.34 (95% CI 1.17–1.53) for those born with a low birth weight and 1.83 (95% CI 1.28–2.62) for those born with a very low birth weight [4]. The association remained significant after adjustment for sex, maternal age, race, country of residence and marital status. Lung function abnormalities were also common following premature birth. High airway resistance and evidence of gas trapping have been reported in infancy especially in those who have wheezing episodes [13]. Lung function improves with increasing age, but longitudinal studies have highlighted that in the first 3 years there was no significant change in air flow limitation [14]. In another study, children who had BPD had airflow limitation at school age. The reductions in FEV_1 and forced mid-expiratory flow at school age showed a significant positive correlation with maximum flow at functional residual capacity data obtained at 24 months of age [15].

Bronchopulmonary dysplasia

BPD is now usually diagnosed when prematurely born infants have an ongoing supplementary oxygen requirement beyond 28 days after birth. It is further classified at 36 weeks post-menstrual age into mild (no longer requiring supplemental oxygen), moderate (requiring $<30\%$ oxygen) and severe (requiring $>30\%$ oxygen and/or positive pressure support) [16]. BPD has been further delineated as "old" or "new" [17]. Old BPD was seen in relatively mature, prematurely born infants who had severe respiratory distress in the neonatal period requiring high pressure ventilation and inspired oxygen concentrations. *Post mortem* examination demonstrated that their lungs were over inflated and there was fibrosis and smooth muscle hypertrophy [18]. By contrast, very prematurely born infants may develop new BPD having suffered only minimal or no initial respiratory distress. At *post mortem*, there are large simplified alveolar structures and a dysmorphic capillary configuration, hence it has been proposed that new BPD is a disruption of the normal processes of alveolarisation [17].

The aetiology of BPD is multifactorial (table 2) and, although occasionally seen in infants born at term with severe respiratory failure, there is an inverse relationship between gestational age and BPD development [19]. High oxygen concentrations have been implicated in the development of BPD. Exposure of developing rat lungs to high oxygen concentrations resulted in large saccular alveoli similar to the changes seen in BPD [20]. Only brief exposure to a high oxygen concentration may be sufficient to initiate a process resulting in BPD. VENTO *et al.* [21] compared the outcomes of prematurely born infants, born between 24 and 28 weeks gestation, who were resuscitated with either 30% or 90% oxygen in the labour suite. Both groups were subsequently weaned to saturation targets of 75% at 5 min and 85% at 10 min. Those resuscitated with 90% oxygen had a significantly higher rate of BPD [21]. Prematurely born infants are particularly vulnerable to oxygen toxicity as they have incomplete development of their pulmonary antioxidant enzyme systems and low levels of antioxidants such as vitamins C and E. However, post-natal use of antioxidants has resulted in variable outcomes [22]. Meta-analysis of randomised controlled trials (RCTs) of vitamin A supplementation has demonstrated a significant, but modest, reduction in oxygen dependency at 36 weeks post-menstrual age, but the vitamin A was administered by repeated intramuscular injections [23].

Mechanical ventilation has also been implicated in the development of BPD. Ventilation of newborn mice for 24 h with air resulted in a 50% reduction in alveolar number with histological features similar to BPD [24]. The likely mechanism of increased BPD development in mechanically ventilated infants is volutrauma. A systematic review of RCTs has demonstrated that volume targeted ventilation is associated with a significantly lower occurrence of BPD compared with pressure limited ventilation [25]. A systematic review of RCTs of prophylactic high frequency oscillatory ventilation (HFOV) *versus* conventional ventilation demonstrated that HFOV was also associated with a significantly lower occurrence of BPD [26]. Follow-up at 11–14 years of age of children entered into one of the RCTs (the UK oscillation study) included in the meta-analysis demonstrated that the HFOV group had significantly better lung function, in particular small airway function, as well as better achievement at school, which suggested they had better visual spatial skills [27]. During HFOV, volumes less than half of those encountered during conventional ventilation are used.

Chorioamnionitis has been implicated in the pathogenesis of BPD. Intra-amniotic injection of endotoxin in sheep resulted in a 30% reduction in alveolar number in prematurely

Table 2. Factors related to the development of bronchopulmonary dysplasia

Predisposition
Immaturity
Genetic
Respiratory distress syndrome
In utero inflammation
Severe lung disease
Patent ductus arteriosus/fluid overload
Pulmonary interstitial emphysema
High level of respiratory support
Volutrauma
Supplementary oxygen
Contributory factors
Post-natal infection
Surfactant abnormalities

delivered lambs [28]. In humans, one study demonstrated that chorioamnionitis was associated with a reduction in the incidence of respiratory distress syndrome, but an increased incidence of BPD [29]. A subsequent study demonstrated that chorioamnionitis was only associated with an increased incidence of BPD if the infants subsequently developed post-natal sepsis or required prolonged ventilation, hence a "double hit" theory was postulated [30]. However, a meta-analysis demonstrated that if gestational age is taken into account there was no significant association between BPD and chorioamnionitis [31]. In addition, no significant differences were found in lung function results at 36 weeks post-menstrual age between infants born prematurely who had or had not been exposed to chorioamnionitis [32].

There is a genetic predisposition to BPD as some infants have a family history and heritability has been estimated to be 50–80% [33]. Certain single-nucleotide polymorphisms (SNPs) have been associated with the development of BPD. The presence of a SNP associated with the *SPOCK2* gene conferred an increased risk of moderate/severe BPD in both Caucasian and French infants of African descent, which was replicated in a Finnish population [34]. Furthermore, it was demonstrated that SPOCK2 mRNA was increased during the alveolar stage of development in rats and that expression was increased following exposure of the rats to hyperoxia [34]. SNPs associated with vascular endothelial growth factor [35], superoxide dismutase [36], matrix metalloproteinase [37] and IL-18 [38] have also been implicated in the pathogenesis of BPD. In a genome-wide association study a SNP of *COL23A1*, a transmembrane collagen expressed in the mesenchyme in the developing lung, was identified as potentially important in BPD [39].

Abnormal antenatal lung growth

Abnormal antenatal lung growth may result in pulmonary hypoplasia, but primary pulmonary hypoplasia is uncommon. Pulmonary hypoplasia is usually secondary to a variety of insults that result in a reduction in either "space" for the lungs to grow, fetal breathing movements or amniotic fluid volume. Conditions leading to a reduction in intrathoracic space include congenital diaphragmatic hernia, pleural effusion and congenital cystic adenomatoid malformation; skeletal abnormalities result in extrathoracic compression. Fetal breathing movements are essential to normal pulmonary development; hence, neurological problems such as Werdnig–Hoffman disease and congenital muscular dystrophy are associated with pulmonary hypoplasia. Reduction in amniotic fluid volume, particularly by early rupture of the membranes prior to 26 weeks of gestation, is also associated with pulmonary hypoplasia. It had been proposed that reduction in amniotic fluid would result in increased extrathoracic pressure and hence impairment of pulmonary development; however, it has been shown that intrauterine pressure is no higher in affected than unaffected pregnancies. Other causes of reduced amniotic fluid volume are fetal renal disease, which can result in a reduction in bronchial branching and decreased alveolar number and size, indicating maldevelopment prior to 16 weeks of gestation [40]. Although not associated with severe pulmonary hypoplasia, amniocentesis in the first or second trimester of pregnancy may affect lung growth leading to an increased incidence of respiratory problems and lung function abnormalities in infancy [41–43]. An explanation for these adverse outcomes is that invasive antenatal procedures may be associated with reduced fetal breathing movements as a result of subclinical infection and raised prostaglandin levels [44]. Pulmonary hypoplasia is more common in infants with trisomy 18 and 21, it can occur in twins and there may be a family history. The outcome of pulmonary hypoplasia varies according to its severity. Those with mild disease have minimal signs of respiratory distress, usually tachypnoea, which

resolves in the first 5 weeks after birth without intervention [45]. However, severe pulmonary hypoplasia is associated with life threatening respiratory failure and pulmonary hypertension.

Intrauterine growth retardation

Among infants born very prematurely, those who had suffered intrauterine growth retardation were more likely to be oxygen dependent at 36 weeks post-menstrual age, have had a pulmonary haemorrhage and/or post-natal steroid requirement, and had a higher mortality rate [3]. In addition, they were more likely to require hospital admission for respiratory problems and have increased cough and use of chest medicine [3]. Very low birth weight (<1500 g) and low birth weight infants (1500–2000 g) have a higher likelihood of hospitalisation for respiratory illness as young adults than those with a birth weight >2500 g [4]. In a case–control study, there was an increased risk of hospitalisation in adulthood in both those born small for gestational age or prematurely, with the risk compounded in those adults born both prematurely and small for gestational age [46].

Intrauterine growth retardation is associated with reduced lung function in infancy [47] and adulthood [10, 48]. BARKER *et al.* [10] studied a large cohort of males born in the UK in the early 20th century and found rates of death from COPD were inversely correlated with birth weight and weight at 1 year of age. The mean FEV_1 at age 59–70 years, adjusted for height and age, increased by 0.06 L (95% CI 0.02–0.09 L) with every 1 lb (450 g) increase in birth weight, independent of smoking habit and social class [10]. In addition, a longitudinal cohort study of infants born at term and followed up until adulthood demonstrated a strong association between low birth weight and reduced lung function, with a linear relationship between birth weight and FEV_1 and FVC [48]. Animal models have demonstrated that fetuses with intrauterine growth restriction have increased thickness of the pulmonary air–blood barrier and fewer alveoli per respiratory unit, suggesting nutritional restriction *in utero* may alter the functional architecture of the developing lung predisposing to disease both early and late in life [49].

Towards the end of the Second World War, a food embargo by Germany in combination with a severe winter resulted in a famine in the Netherlands, which peaked between December 1944 and April 1945. During this period daily rations fell to between 400 and 800 calories. Following surrender by the Germans in 1945, food became available and by June 1945 rations were more than 2000 calories per day. In one study, 2414 infants born between November 1943 and February 1947 were followed up to 50–58 years of age. Those exposed to famine *in utero* had a lower birth weight and were found to be at greater risk of renal impairment, coronary heart disease, breast cancer and obstructive airway disease [50]. Elevated lipid levels in males exposed to famine *in utero* [51] and higher systolic and diastolic blood pressure in the famine exposed group [52] have also been reported. However, a subsequent study in the same cohort found no significant differences in the incidences of coronary artery disease and ECG abnormalities between the prenatally famine exposed and unexposed groups [53]. A study investigating the transgenerational effects of nutritional deprivation *in utero* found higher weight and higher BMI in the offspring of males exposed to famine *in utero* compared with those unexposed to famine, but there were no significant differences in the offspring of females or in self-reported health between the exposed and unexposed groups [54]. The cohort is being further followed up to determine the effect of exposure to famine *in utero* on a number of markers of ageing including cognitive decline, the incidence of white matter hyperintensities and cerebral microbleeds on magnetic resonance imaging, incidence of fractures, grip strength and physical performance, and visual

acuity. Possible underlying mechanisms, such as telomere length, oxidative stress and inflammatory status, are also being explored [55].

Prenatal antioxidant supplementation might be expected to influence fetal lung growth and development and reduce the oxidative stress implicated in the development of BPD. Prenatal vitamin E treatment improved lung growth in rats [56], and in birth cohort studies, a lower maternal intake of vitamin E was associated with higher prevalence of early childhood wheezing [57, 58]. Follow-up of infants entered into a randomised trial, however, did not demonstrate improved infant respiratory outcomes following maternal high dose vitamin C and E supplementation [59]. A meta-analysis of 62 studies examining the effect of diet on the development of allergy and asthma in childhood, however, found that high maternal dietary vitamin D (OR 0.56, 95% CI 0.42–0.73) and E (OR 0.68, 95% CI 0.52–0.88) intake during pregnancy was associated with a reduced risk of wheeze [60]. Maternal vitamin D deficiency at 16–20 weeks of gestation has been found to correlate with FVC and FEV_1 at 6 years of age [61]. By contrast, the use of folate supplements in pregnancy has been associated with a significant increase in wheeze, respiratory tract infections and respiratory hospitalisation [62]. Maternal ingestion of certain medications may also increase respiratory morbidity. Meta-analysis of the results of six studies demonstrated children aged from 30 to 84 months whose mothers had taken paracetamol during any stage of pregnancy had an increased risk of current wheeze (OR 1.21, 95% CI 1.02–1.44) [63].

Maternal smoking during pregnancy

Maternal smoking is a risk factor for intrauterine growth restriction [64] and premature birth [65] both of which influence long-term respiratory outcome, but it may also have a direct effect on lung development. Administration of nicotine to pregnant rhesus monkeys resulted in lung hypoplasia and reduced surface complexity of developing alveoli [66]. In children less than 2 years of age, the risk for lower respiratory illness was increased by 72% if their mother smoked [5]. A history of maternal smoking, as reported by the offspring, was associated with their increased respiratory symptoms even in adulthood [67].

Exposure of pregnant rats to nicotine resulted in fewer enlarged air saccules in nicotine exposed pups, which resulted in reduced respiratory reserve compared with controls [68]. Similarly, mice exposed to nicotine *in utero* had reduced forced vital capacity and increased airway length but reduced diameter [69]. Hence, lung function abnormalities might be expected in infants, but studies examining the effect of maternal smoking in pregnancy on newborn lung mechanics have yielded variable results [70]. For example, in one study a significant increase in resistance was found in girls born to mothers who smoked in pregnancy, while a significant reduction in compliance was found in boys born to mothers who smoked in pregnancy [71]. In adolescents and young adults, however, reductions in lung function have been reported. Follow-up of the Western Australian pregnancy cohort at 14 years found reduced FEV_1 and FEV_1/FVC in the children of mothers who smoked in pregnancy with an increased risk of current asthma, wheeze and exercise-induced wheeze [6]. Spirometry results from 2409 young adults highlighted that *in utero* exposure to smoking was associated with reduction in FEV_1 and forced expiratory flows between 25% and 75% of FVC in males, although not females [72]. The results of a longitudinal study have demonstrated that wheeze at 18 years was only associated with *in utero* smoking in those who had impaired lung function during infancy [73], suggesting those with poorer lung function in infancy had an increased vulnerability to further insults. Smoking during pregnancy rather than post-natally results in greater respiratory morbidity. GILLILAND *et al.* [74] assessed airway function

in 5933 children aged 7–18 years and found significant reductions in airway function in those exposed to smoking antenatally, but not in those exposed to passive smoking post-natally. This impairment was greatest in those exposed to smoking *in utero* and who developed early-onset asthma, defined by parental report of physician-diagnosed asthma before 5 years of age [74]. Similarly, hospital admissions due to LRTI and episodes of bronchitis in the first 5 years after birth were more common in infants of mothers who smoked only during pregnancy compared with those of mothers who smoked only after pregnancy [75]. Furthermore, the risk of admission to hospital for any cause in the first year after birth was significantly higher for infants whose mothers who smoked during pregnancy (OR 1.27, 95% CI 1.24–1.29) compared with infants of nonsmokers [76].

Infants of smoking mothers have been shown to have a reduced response to added dead space, which may reflect impaired respiratory control [77]. Maternal smoking *in utero* exposes the fetus to toxins such as nicotine, carbon monoxide and cadmium. Prenatal nicotine exposure results in cell death in the brainstem of animal models. It may also cause fetal hypoxia as nicotine is a powerful vasoconstrictor reducing blood flow to the uterus. Nicotine is also a teratogen. These factors may result in neurodevelopmental abnormalities adversely affecting infant respiratory control [77].

Mode of delivery

Both the mode (vaginal or caesarean section) and need for delivery (emergency or planned) may impact on infant and childhood respiratory outcomes. The risk of neonatal respiratory morbidity was reported to be significantly greater when infants were delivered by caesarean section when not in labour compared with caesarean section when in labour (OR 2.9) and vaginal delivery (OR 6.8) [78]. The increased risk associated with caesarean section when not in labour increased for each week prior to the 39th week of gestation [78]. A meta-analysis of the results of 23 studies reported an increased risk of childhood asthma following caesarean section (OR 1.22, 95% CI 1.14–1.29) [79]. Infants born by caesarean section were also found to be at greater risk of developing food allergies at 1 year of age (OR 2.06, 95% CI 1.123–3.80) [7] and type 1 diabetes (OR 1.19, 95% CI 1.04–1.36) [8]. It has been argued that the increased incidence of immune-related disease may result from the different bacterial exposure during caesarean section affecting the normal development and sensitisation of the infant immune system [80]. Delivery by caesarean section has also been found to increase the risk of obesity in childhood [81].

Respiratory viral infections

Infection with RSV occurs in almost all children by 2 years of age and results in hospitalisation in approximately 1% of healthy term infants. The hospitalisation rate is higher in those with pre-existing medical conditions including those born prematurely particularly if they developed BPD. RSV LRTIs have been reported to be associated with increased asthma and wheeze throughout childhood and into adulthood [82, 83]. Lung function abnormalities, reductions in FEV_1 and FEV_1/FVC have been reported in young adults [84]. There is, however, evidence to suggest that infants with premorbid lung abnormalities may be at greater risk of severe RSV infection requiring hospitalisation [85]. There may also be a genetic predisposition to symptomatic RSV LRTIs [86].

Other viral infections in infancy also contribute to respiratory morbidity. For example, respiratory health-related costs were increased in prematurely born infants who suffered a

rhinovirus infection [87]. A longitudinal study has demonstrated reduced lung function at 1 year in premature babies who had LRTIs due to a variety of respiratory viruses, including RSV and rhinovirus [88]. Adenovirus infection can result in severe respiratory morbidity, including bronchiectasis and lung function abnormalities [89]. Human metapneumovirus bronchiolitis in infancy has been reported to be strongly related to asthma at 5 years of age [90]. In the Tennessee study, infants born 4 months prior to the winter viral season were 30% more likely to develop childhood asthma than those born 12 months before the peak, suggesting a role of viral infections [91].

Epigenetics

Epigenetics describes the processes that influence the transcription and expression of specific genes [92]. Modification of the DNA itself or the histone, the scaffold upon which genetic material is structured, controls identification of and access to specific regions and allows modulation of gene expression [93]. This modification allows critical alterations in activity to occur at different stages of development at the gene level in response to cellular signals [94]. The mechanisms by which these processes occur are beyond the scope of this chapter, but are summarised elsewhere [93].

The mechanism by which epigenetics may contribute to altered lung development is not fully understood, but possible components of the pathway have been identified. The peroxisome proliferator-activated receptor (PPAR)γ is crucial to normal lung development [95]. The expression of the gene, in association with altered gene methylation, is inhibited in the rat lung by intrauterine growth retardation [96]. Alterations in the levels of PPARγ are associated with changes in elastin mRNA transcript levels [97]. The morphological features of animal models of intrauterine growth restriction, maternal tobacco smoking and mechanical ventilation are similar, in that they involve altered alveolar formation. In all of these models there is reduced lung expression of elastin, which is crucial for alveolarisation. Mild protein deficiency in pregnant rats results in altered methylation of cytosine–phosphate–guanine (CpG) islands around, and reduced expression of, the *Wnt2* gene [98]. Wnt2 has been shown to be critical to vascularisation of the placenta, and *Wnt2* deficient mice are low birth weight and have increased perinatal mortality. Increased methylation of promoter sites of the *Wnt2* gene in humans has been found in the placenta of infants small for their gestational age [99].

Exposure to cigarette smoke condensate results in dose-dependent histone modification of bronchial epithelial cells [100], and maternal smoking results in global methylation alterations in the buccal cells of their children [101]. There is evidence of a transgenerational effect of smoking. An association has been reported between the maternal grandmother smoking in pregnancy and an increased risk of asthma in the grandchild, without the mother smoking in pregnancy [102]. In addition, pregnant rats exposed to nicotine had offspring with an increased total respiratory system resistance and reduced dynamic compliance following methacholine challenge, the male pups also had increased tracheal constriction following acetylcholine challenge. Examination of their lung tissue revealed increased contractile protein content of the lung, increased fibroblasts, reduced PPARγ expression and increased histone 3 acetylation [103]. The pups were bred to give second generation pups, but without further nicotine exposure, and the lung function and histological changes in the second generation pups were consistent with the first generation pups. These results suggest that nicotine-induced epigenetic changes in the fetus may become permanent and incorporated into the germ line, and hence affect subsequent generations. The changes in compliance, resistance and histone 3 acetylation following nicotine exposure were inhibited

by administration of rosiglitazone, a PPARγ agonist, suggesting that this gene may play a critical role in nicotine-induced lung injury [103]. In a further study, increased parenchymal deterioration and emphysema were demonstrated in both the first (F1, exposed to nicotine *in utero*) and second (F2, unexposed) generation rats. F2 rats resulting from one exposed and one unexposed F1 rat showed similar findings, irrespective of whether the mother or father was exposed to nicotine *in utero,* demonstrating the heritability is *via* both the male and female germ lines [104]. To determine whether epigenetic modification in infants of mothers who smoked was inherited from the maternal germ line or resulted from *in utero* exposure to methylation the methylation of 26 CpG sites previously identified as affected by maternal smoking were examined. Abnormal methylation was seen only in infants where the mother smoked beyond 18 weeks gestation; there was normal methylation if the mother had ceased smoking prior to pregnancy or smoked only in the first trimester [105]. This suggests that these epigenetic changes occur as a result of *in utero* exposure, but as the changes may be passed on to subsequent generations it seems likely that the fetus is vulnerable to incorporating epigenetic changes that may enter the germ line.

Methylation and histone modification is crucial to the differentiation of T-helper cells, with persistence of histone modifications down cell lineages. Maternal diet during pregnancy may alter immune development and vulnerability to atopy *via* epigenetics. Folate is a potent methyl donor, and could modify genetic expression through increased methylation. Indeed, an association between maternal folate supplementation and increased atopy in offspring has been demonstrated [62]. In addition, the offspring of mice given a methyl rich diet during pregnancy had increased allergic airway disease, with increased methylation and reduced expression of Runt-related transcription factor, a gene implicated in downregulation of airway reactivity [106].

Furthermore, although gene expression profiles from $CD4^+$ T-cells did not differ between eight adults with seasonal allergic rhinitis and eight controls, the genome-wide DNA methylation profile distinguished those with seasonal allergic rhinitis from controls [107].

Viral infection in infancy, particularly RSV infection, is a major risk factor for childhood asthma. Attempts to test the hypothesis that RSV infection in infancy may predispose to wheeze *via* epigenetic mechanisms have been limited as the virus is human specific. Nevertheless, in a mouse model of virus-induced hypersensitivity due to neonatal pneumovirus infection, which was followed by pulmonary sensitisation to ovalbumin, altered epigenetic markers across a range of genes implicated in mediating inflammatory responses were demonstrated. There was reduced methylation and increased expression of IL-4 and interferon-γ in pulmonary $CD4^+$ T-cells [108].

Environmental factors, including air particulates [109] and traffic-related polycyclic aromatic hydrocarbons [110], that contribute to the development of childhood asthma have been shown to alter gene methylation. Maternal exposure to traffic pollution strongly correlated with increased methylation of a CpG island of the acyl-CoA synthetase long chain family member 3 in placental tissue and cord blood. Furthermore, the increased methylation correlated both with high maternal pollution exposure (OR 13.8; $p<0.001$) and parental report of asthma symptoms in the child before the age of 5 years (OR 3.9; $p<0.05$) [110].

Conclusion

Chronic respiratory morbidity, including asthma is common in childhood. Many early life events increase the risk of this adverse outcome and there is increasing evidence that

epigenetics may contribute. Longitudinal studies are required to further understand how early life events may regulate transgenerational epigenetics and lead to asthma.

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Active and passive tobacco smoking

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Despite reduction in prevalence of active smoking since 1980, the absolute number of smokers has increased worldwide from 718 to 967 million in 2012. In Europe, the prevalence of smoking in 2012 ranged from 13% to 40%, with higher values in south and east. Trends in smoking-related mortality and morbidity follow changes in prevalence; control of smoking prevents premature death and smoking cessation is associated with longer life. Research on the relationship between smoking and health is still in progress: 10 new diseases causally linked to active smoking were introduced in the 2014 US Surgeon General's Report, along with enhanced causality for TB and idiopathic pulmonary fibrosis. There is no safe level of exposure to passive smoking. Authoritative health organisations agree that passive smoking exposure leads to serious and fatal diseases, including cardiovascular and respiratory diseases, and cancers. Children, including fetuses and newborns, can develop health effects from exposure. About 35% of nonsmokers are exposed worldwide to passive smoking at home, at work and in public places.

In the previous *Monograph* on respiratory epidemiology, SLAMA [1] carefully described the trend of smoking prevalence within a population and proposed a model curve of smoking evolution, in five phases. Each phase corresponds to different proportions of smokers, ex-smokers and nonsmokers; over time, different countries or subgroups of a population can be allocated to different points on this curve. Currently, some developed countries are in the plateau phase (third phase), many have experienced a drop in total prevalence (fourth phase) and very few are in the last phase (new smokers below 10%) [2]; the majority of the developing countries are in the initial phases, characterised by a rising of current smoker prevalence [3].

According to World Health Organization (WHO) figures, globally, smoking remains one of the most important health problems [4]. Because of the dramatic burden of smoking on respiratory diseases and the active role of pulmonary physicians in smoking interventions, knowledge of the epidemiological burden of smoking is crucial in their training and continuing education. Since its foundation in 1990, the European Respiratory Society (ERS) has largely contributed to disseminating awareness of the health risks of smoking, as well as the need for and possibility of doctors helping smokers who are willing to quit. In addition, the ERS has been advocating a smoke-free Europe. The ERS published several comprehensive documents [5], and regularly updates data and information on this topic [6, 7]. The aim of this chapter is to outline the emerging evidence on active and passive smoking, providing an

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update on European and worldwide prevalence rates. Emphasis will be placed on definitions and characteristics of passive smoking exposure, and the impact of tobacco control policy.

Prevalence of active smoking in Europe

Prevalence of smoking in Europe during 2012 is shown in table 1. The data are derived from the European Commission Eurobarometer report (27 countries) [8] except for the countries not included in the Eurobarometer surveys, where the source was the Organisation for Economic Co-operation and Development (OECD) Health Data [9]. The lowest proportion of smokers was observed in Sweden (13%) and the highest in Greece (40%); overall, the prevalence was higher in the south and east than in the north and west. According to the OECD Health Data [9], smoking prevalence among males was higher than in females in all European countries (during 2010) except in Sweden; in the other Nordic countries, as well as in UK, male and female smoking rates were close to equal (table 2). Indeed, the sex gap in smoking rates was large in Latvia, Lithuania, Cyprus, Bulgaria, Romania and Turkey.

Although large differences remain in smoking prevalence, smoking rates across European countries have declined in the last decade, with the exception of the Czech Republic; on average, prevalences have decreased by about 5% since the year 2000, with a faster decline among males than females [9].

Inter-country comparability is affected by methodological problems in data collection related to sample selection, sample size, response rate, questionnaire administration and the kind of questions asked [10]. Comparison between the 2006 Eurobarometer study and contemporaneous national surveys showed that European Union (EU) prevalence estimates (which are the only available indicator of smoking prevalence in some areas of Europe) were different from the national estimates. On average, the overestimation was +0.37%, with some discrepancies (*e.g.* national estimates for Slovakia were 13% higher than Eurobarometer,

Table 1. Smoking prevalence in Europe, in 2012

Country	Total smokers	Country	Total smokers
Austria	33	**Lithuania**	30
Belgium	27	**Luxembourg**	27
Bulgaria	36	**Malta**	27
Cyprus	30	**The Netherlands**	24
Czech Republic	29	**Norway#**	19
Denmark	26	**Poland**	32
Estonia	26	**Portugal**	23
Finland	25	**Romania**	30
France	28	**Slovakia**	23
Germany	26	**Slovenia**	28
Greece	40	**Spain**	33
Hungary	32	**Sweden**	13
Iceland#	14	**Switzerland#**	20
Ireland	29	**Turkey#**	25
Italy	24	**UK**	27
Latvia	36	**European average**	**28**

Data are presented as %. #: in 2010. Data from [8, 9].

Table 2. Smoking prevalence in Europe in males and females, in 2010

Country	Male smokers	Female smokers	Country	Male smokers	Female smokers
Austria	27	19	**Lithuania**	43	15
Belgium	24	18	**Luxembourg**	21	16
Bulgaria	40	19	**Malta**	24	15
Cyprus	38	14	**The Netherlands**	23	19
Czech Republic	30	19	**Norway**	19	19
Denmark	20	20	**Poland**	31	18
Estonia	37	19	**Portugal**	27	11
Finland	23	16	**Romania**	33	9
France	26	21	**Slovakia**	27	13
Germany	26	18	**Slovenia**	22	16
Greece	38	26	**Spain**	31	21
Hungary	32	22	**Sweden**	13	15
Iceland	15	14	**Switzerland**	23	18
Ireland	31	27	**Turkey**	12	39
Italy	30	17	**UK**	22	21
Latvia	46	13	**European average**	**29**	**18**

Data are presented as %. Data from [9].

while the UK national estimate was 10% lower) [10]. Yet, accounting for the methodological limitations, there are still considerable differences in smoking prevalence across Europe, and in male *versus* female and current *versus* ex-smoking prevalence [11]. Eastern European lower income countries and those with less advanced tobacco control policies have less favourable smoking patterns and are at an earlier stage of the tobacco epidemic.

Trends in active smoking-related diseases

Smoking-related mortality and morbidity reflect the smoking epidemic curve, which has a latency period related to the natural history of the specific diseases [12]. Updating the global perspective, NG *et al.* [13] used data from more than 2000 international reports (189 countries) to derive estimates of cigarette smoking rates and intensity between 1980 and 2012. Although prevalence estimates decreased for both males (from 40.8% to 31.1%) and females (from 10.7% to 6.2%), the rate of decline has slowed since 2006. In addition, due to overall population growth, the absolute number of smokers has increased, from 718 to 967 million globally. As a consequence, the estimates of the annual tobacco-related deaths now exceed 5 million worldwide and are expected to rise to over 10 million in a few decades [14, 15]. In US population surveys, THUN *et al.* [16] analysed the mortality trends across three time periods (1959–1965, 1982–1988 and 2000–2010): in never-smokers, the age-standardised rates of death from any cause were 50% lower in the 2000–2010 than in 1959–1965; in contrast, female smokers received no benefit and male smokers showed only a 24% reduction. Relative risks of lung-cancer death among smokers were almost five times as high for males in the 1959–1965 cohort, but in the 2000–2010 cohort, the risks had equalised and increased. Male and female current smokers had similar relative risks of death from COPD (25.61 for males and 22.35 for females), ischaemic heart disease (2.50 for males and 2.86 for females), any type of stroke (1.92 for males and 2.10 for females) and all causes combined (2.80 for males and 2.76 for females). The risk of death from cigarette smoking

continues to increase among females and the increased risks are now nearly identical for males and females, compared with never-smokers. Among males, the risks associated with smoking have plateaued at the high levels seen in the 1980s, except for a continuing increase in mortality from COPD. In the EU, lung cancer kills more people than any other cancer, accounting for about 20% of all cancer deaths; smoking is the main cause of COPD (in some parts of the world, exposure to biomass fuels is relatively more important) [6].

While tobacco-attributable mortality increases slowly after the uptake of smoking, the effects of cessation emerge more rapidly [17, 18]. Those who began smoking in early adulthood but stopped before the age of 40 years avoided more than 90% of the excess risk during their next few decades of life, as compared with those who continued smoking; even those stopping at the age of 50 years avoid over half of the excess risk, although substantial hazards persist [17–20].

In a recent issue of *JAMA* entirely dedicated to tobacco control (published in the 50th anniversary of the first US Surgeon General's report in 1964; see later), HOLFORD *et al.* [21] analysed data on the cigarette smoking histories of the US adult population in 1964–2012. Using data from multiple surveys, they estimated the number of lives saved between 1964 and 2012 by comparing the actual death rates to those that would have occurred if smoking prevalence trends had remained the same as before the first Surgeon General's Report. There were 17.6 million smoking-attributed deaths during that period, while 8 million premature deaths were prevented due to tobacco control measures.

Modelling population data allows estimation of the impact of changing smoking patterns on public health, and can be used to implement better and focus smoking control policies. For example, in Italy, the effects of age, time period, and birth cohort on trends of Italian former smokers have been investigated as a reflection of smoking cessation policies by modelling prevalence trends of former smokers [22]. Predicted future trends of the prevalence of former smokers using a Bayesian approach have also been also estimated. There has been a constant increase in the prevalence of former smokers in Italy since the 1980s, in all generations and age groups. Projections of future trends showed a further increase in the number of former smokers in future decades, with an estimate of the "end of smoking" around the years 2060 and 2055 in males and females, respectively. Furthermore, different scenarios of prevention can be evaluated for specific causes of death, considering various interventions [23]. An early decrease in lung cancer and respiratory diseases could be achieved by annual computed tomography screening programmes, followed by a drop in all-cause smoking-attributable deaths in subsequent decades due to tobacco control policies. Another newly developed tool has quantified the changes in population respiratory health (smoking-related cancer and COPD/asthma) potentially resulting from modifying the population distribution of exposure to smoking [24]. This tool is based on the epidemiological measure of the population attributable fraction; it estimates the impact of scenario-based distribution of smoking on inequalities in mortality. Countries with smaller inequalities in smoking have smaller inequalities in mortality, with smoking playing an important part in the explanation of inequalities. Over half of the relative inequalities may be reduced for some causes of death in Europe by modifying the population distribution of exposure to smoking [24]. Reducing the health burden of tobacco smoking involves both treatment and prevention. As the latency period for most smoking-related diseases lasts over 20 years, the most effective tool for reducing morbidity and mortality is legislation aimed at reducing the uptake of smoking among young people [6].

Epidemiological data on the health impact of smoking variations can also be used at an individual level. Recently [25], we quantified gain in life-years associated with quitting

smoking by number of cigarettes smoked per day, for both Italian males and females. By using individual information on sex, age and numbers of cigarettes smoked per day, it is possible to estimate, for a single smoker, the additional number of years they can live if they quit at once, thus providing a personalised health message to promote a quit attempt. Italian male and female quitters gain noteworthy life expectancy, regardless of quitting age and number of daily cigarettes smoked at cessation time. The more cigarettes per day a male or female smokes and the younger their age of quitting smoking, the more the years of life they gain from cessation. When a male or a female who smokes fewer than 20 cigarettes per day quits before 35 years of age, they gain a life expectancy similar to that of a never-smoker. For the same number of cigarettes smoked per day, survival proportions are lower for male than female former smokers who quit after the age of 35 years. Quitting smoking at older ages determines a lower benefit, even though gains in life expectancy are still remarkable, especially for heavy smokers; a male or female who smokes over 20 cigarettes per day could gain up to 6 or 4 years of life, respectively, if they quit smoking between the ages of 55 and 64 years.

New insights into active smoking epidemiology

The 2014 Surgeon General's Report

Despite the wealth of established results, research on the relationship between smoking and health, in terms of either damage or benefit of cessation, is still ongoing. The most important event of 2014 in the field of tobacco smoking epidemiology was the 32nd US Surgeon General's Report [26], describing the dramatic evolution of knowledge of the health consequences of smoking since the first report issued in 1964. The reports of the Surgeon General have developed a formal framework for assessing evidence of disease causation while describing the working methods and the criteria used to make inferences about cause–effect relationships. Five criteria have to be applied: consistency, strength, specificity, temporal relationship and coherence. Accordingly, 37 different conditions are causally linked to smoking; eight chronic diseases (age-related macular degeneration, congenital defects caused by maternal smoking (orofacial clefts), TB, diabetes, ectopic pregnancy, male sexual function disorders (erectile dysfunction), rheumatoid arthritis and immune function disorders) and two cancers (liver and colorectal) are new diseases causally linked to smoking in the last Report [26].

Regarding respiratory diseases, the new report gives important conclusions on the relationship between smoking and TB, and interstitial lung diseases [26]. A causal relationship has been established with increased risks of *Mycobacterium tuberculosis* disease and TB mortality; evidence is suggestive of a causal link between smoking and a risk of recurrent TB. This result is noteworthy in view of the distribution of TB epidemics in countries in which smoking prevalence is still growing: effective and efficient cessation strategies need to be determined, targeting the epidemiology and smoking behaviours of the different populations. Within the heterogeneous group of interstitial lung diseases, the evidence on risk associated with cigarette smoking has been variable. However, a causal association with idiopathic pulmonary fibrosis is considered very suggestive (even if not sufficient), due to the strong biological plausibility and the consistency of epidemiological results (in different populations, from different countries and over different periods of time).

Regarding lung cancer, the risk of developing adenocarcinoma from cigarette smoking has increased since the 1960s, in part in relation to changes in the design and composition of cigarettes (like ventilated filters) since the 1950s. Decline of squamous cell carcinoma has followed the trend of declining smoking prevalence.

Sex equality

In the Report [26], emphasis has been given to sex-related results. The disease risks for females have risen sharply over the last 50 years and equal those of lung cancer, COPD and cardiovascular diseases in males. Particularly for COPD, evidence of female susceptibility to developing severe disease at younger ages is considered suggestive (but not sufficient).

Important recent insights have come from epidemiological studies throughout the world. In the European prospective study of 1 million females in UK published in 2013 [18], the first generation of UK females who have smoked a substantial number of cigarettes throughout their adult life, like males, *i.e.* those born around 1940, shows hazards and benefits similar to male smokers, confirming the prediction that if females smoke like males, they will die like males [27]. Measuring temporal trends in mortality across three time periods (1959–1965, 1982–1988 and 2000–2010), THUN *et al.* [16] have shown relative risks of lung-cancer death in male smokers to be almost five-fold higher than in females in the 1959–1965 cohort; in the 2000–2010 cohort, the risks had equalised between the sexes. 25-year-old females interviewed between 1997 and 2004 in the US National Health Interview Survey represent the first generation in the USA in which those who smoked began early in life and continued for decades; for these females, JHA [14] found a tripled relative risk of death and a reduction in survival of at least a decade as for males. In the 1920–1945 Japanese cohort (in which males and females started smoking before the age of 20 years, and consumed a similar number of cigarettes per day), those who continued smoking had an overall mortality that was more than double that of never-smokers in both sexes and a life expectancy reduced by almost a decade (8 years for males and 10 years for females) [20].

Finally, even though this chapter is focussed on tobacco smoke, it is useful to include short considerations on the pervasive phenomenon of electronic cigarettes (e-cigarettes) [28]. 2 years ago, the ERS did not approve any nicotine delivery products, including emerging products such as e-cigarettes, and underlined the potential health risks associated with their usage and exposure [29]. The ERS did not classify e-cigarettes as a safe alternative to smoking nor did it consider them an approved cessation tool. Other documents and position papers have been published or made known by national or international scientific societies and organisations [30]. However, few studies with large sample sizes have been conducted [31–33]. In the recent *JAMA* issue dedicated to the 50th anniversary of the 1964 Surgeon General's Report, ABRAMS [34] summarised both the "promise" of e-cigarettes as a technology that can help smokers to reduce and quit smoking, as well as their dangers as a potential gateway to cigarette smoking. The message for the health professionals is that e-cigarettes should be regulated in the context of stronger evidence about both potential harms and benefits. The best health advice for smokers is to quit; in the harm reduction strategy, e-cigarettes may be proposed in selected subgroups of "hard" smokers (*e.g.* psychiatric patients).

Passive smoking: definition, constituents and properties

Passive smoking, also called involuntary smoking or environmental tobacco smoke, is a common indoor pollutant originating from tobacco combustion of cigarettes and other tobacco products, and from smoke exhaled by smokers [35]. Recently, it was suggested by the WHO Tobacco Free Initiative to avoid using terms such as environmental tobacco smoke, passive smoking and involuntary smoking, and to replace them with the term "second-hand smoke" (SHS). Indeed, the term environmental tobacco smoke seems to suggest that tobacco smoke may be treated as background or ambient (the term was originally introduced by the

tobacco industry). As for "passive smoking" or "involuntary smoking", these terms, often used to describe the exposure to tobacco smoke, suggest that passive or involuntary exposure is not acceptable, but that voluntary or active exposure to tobacco smoke is acceptable. Thus, SHS seems a preferable term emphasising the involuntary nature of the exposure [35].

On May 8, 2014, the ERS and the European Lung Foundation launched a new website providing scientific evidence on the health hazards of active and passive smoking. The website also contains a list of key recommendations for policy-makers about how these harms can be reduced and the health of European citizens protected.

Scientific evidence proved that there is no safe level of exposure to SHS. WHO and other important global health organisations agree that SHS exposure leads to serious and often fatal diseases, including cardiovascular and respiratory disease as well as lung and other cancers. Children, including fetuses and newborns, can also develop health effects from exposure to SHS [36]. Each year, more than 600 000 nonsmoker deaths occur from SHS exposure. For World No Tobacco Day 2014, a call on countries to raise taxes on tobacco has been launched [37].

Recently, a new concept in the field of tobacco control has emerged: so-called "third-hand smoke" (THS) [38]. THS consists of pollutants that remain on surfaces and in dust after the cigarette has been extinguished. Thus, indoor surfaces can represent a reservoir of THS constituents even hours or days after the cessation of active smoking. Human exposure to THS pollutants has not yet been thoroughly studied, especially in relation to more susceptible categories (*i.e.* infants, children and the elderly) who are more at risk of THS exposure/effects than others due to age-specific daily activity patterns [39].

The principal component of SHS is sidestream smoke emitted from the smouldering end of the cigarette. Other components of SHS are exhaled mainstream smoke and mainstream smoke emitted at the mouthpiece as the smoker inhales. Once released into the environment, the components of SHS are diluted and transported by the ambient air [40].

Cigarette smoking is the main source for SHS exposure as it is the most common form of tobacco smoking, although specific geographic variations occur. Tobacco smoke is an aerosol composed of thousands of chemicals released during burning as gases, vapours and particles. At least 250 chemicals in SHS are known to be toxic or carcinogenic agents [40, 41]. However, the health effects of exposure to SHS cannot be estimated from any individual constituents. As SHS is a complex mixture of constituents and exposure to this mixture may be more relevant in terms of health effects than exposure to any individual substance, the assessment of the effects of SHS is usually based on epidemiological studies using exposure to SHS as a whole [40].

Most exposures to SHS take place in homes and workplaces. However, exposure also continues to occur in public places such as restaurants, bars and clubs, as well as multiunit housing and vehicles [42].

Prevalence of passive smoking

Public health impact is evaluated on the basis of the size of the risk of health effects related to SHS and of the occurrence of exposure, intended as both the prevalence rate of SHS, and the levels and duration of exposure in different populations [41].

SHS is the largest contributor to indoor particulate matter, accounting for as much as 50–90% of the total particulate matter concentration [6]. Thus, several studies have used particulate matter <2.5 μm in diameter ($PM_{2.5}$) as an indicator of SHS exposure [43, 44]. In recent decades, some large studies have reported the prevalence of SHS exposure across many countries.

Prevalence in adults

According to a retrospective analysis of worldwide data from 192 countries during 2004, 33% of male nonsmokers and 35% of female nonsmokers are exposed to SHS. The highest prevalences of exposure were estimated in Europe, the western Pacific and region B (WHO-approved classifications: B, low child mortality and low adult mortality) of southeast Asia, with more than 50% of exposed people. Prevalence of SHS exposure was lower in the Americas and the eastern Mediterranean region (about 25%), and lowest in Africa (about 10%) [45].

Figure 1 shows that in Europe, SHS exposure ranges from about 8% in Sweden to 68% in Greece and the Russian Federation [40]. According to the 2012 Eurobarometer report [8], 23% of EU citizens are exposed to SHS in drinking establishments (*i.e.* bars and pubs) and

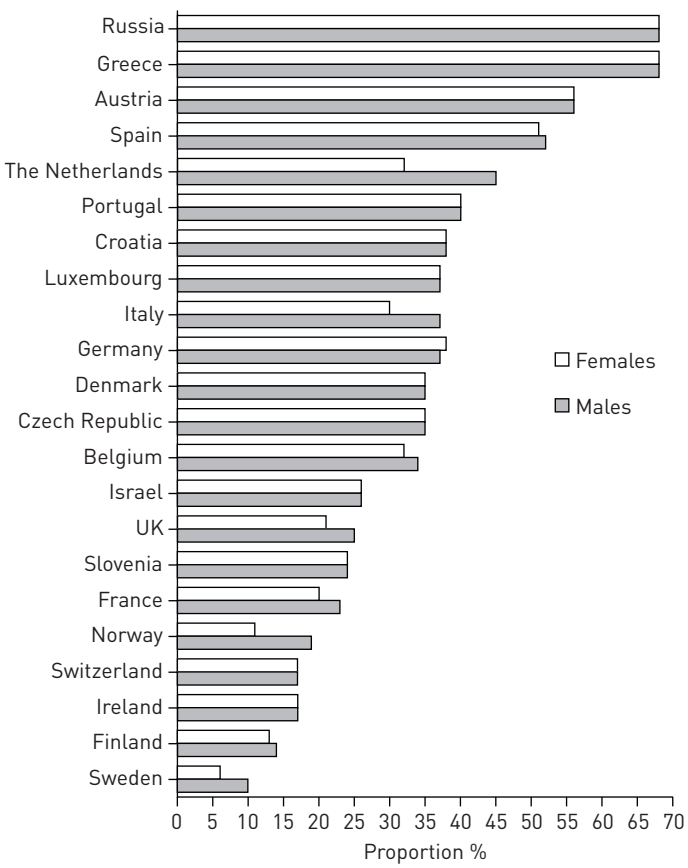

Figure 1. Proportion of adults regularly exposed to second-hand smoke in a selection of European countries. Data from [40].

12% in eating places (*i.e.* restaurants). The highest prevalence rates of SHS exposure in drinking establishments are in Greece, Bulgaria and Luxembourg (about 70%). In contrast, Sweden (3%), the UK (6%), Lithuania (8%), Ireland (8%) and Finland (9%) have the lowest rates of exposure. As for SHS exposure in eating places, high figures are observed in Greece (72%), Bulgaria (57%) and the Czech Republic (55%), while the lowest rates occur in Sweden (1%), Slovenia, Lithuania (both 2%), Finland and the UK (both 4%) [8]. 28% of EU citizens are exposed to SHS indoors at their workplace, mainly smokers (35%), males (33%) and young people (15–24 years) (32%) (fig. 2). Smokers are more likely to be exposed for several hours a day (10%) than nonsmokers (4%). Even in this case, large variations can be observed between EU member states, with the highest prevalence rates of SHS exposure in the workplace in Romania (62%) and Greece (58%), and the lowest figures in Sweden (7%), the UK (9%), Slovenia (13%) and Denmark (13%) [8].

Worldwide, in 2007, it was reported that SHS exposure in cars ranged from 29% in the UK and Australia to 44% in the USA [46].

Prevalence in children

The same worldwide retrospective analysis based on 2004 data reported a prevalence rate of SHS exposure of 40% of children, with the highest value in the western Pacific countries (about 60%) and the lowest value in Africa (about 13%) [45]. Figure 3 shows that in Europe, prevalence of SHS exposure ranges from 7% in Finland to 67% in Greece [40]. In the UK, around 50% of children are estimated to be exposed to SHS in the home, and between 6.5% and 20% of children are reported to be exposed to SHS in cars, with up to 35% of children whose parents are smokers. SHS is therefore a major hazard to the health of millions of children worldwide. Children from socioeconomically disadvantaged backgrounds are generally more heavily exposed to SHS [47]. In Spain, SHS exposure in vehicles is 6%; usually, the driver is a male over 40 years old [48]. Smoke-free cars are more common among nonsmokers than smokers; however, in the Netherlands, 36% of smokers allow smoking in cars carrying children [49]. In the UK, travelling in a car where smoking is allowed is

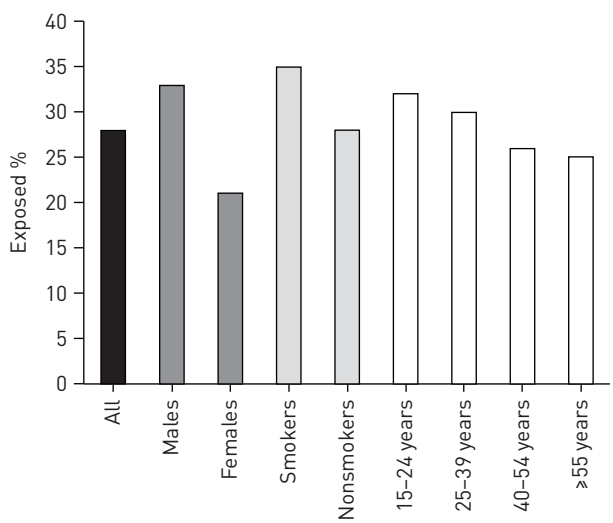

Figure 2. Proportions exposed to tobacco smoke at work in the 27 European Union member states. Data from [8].

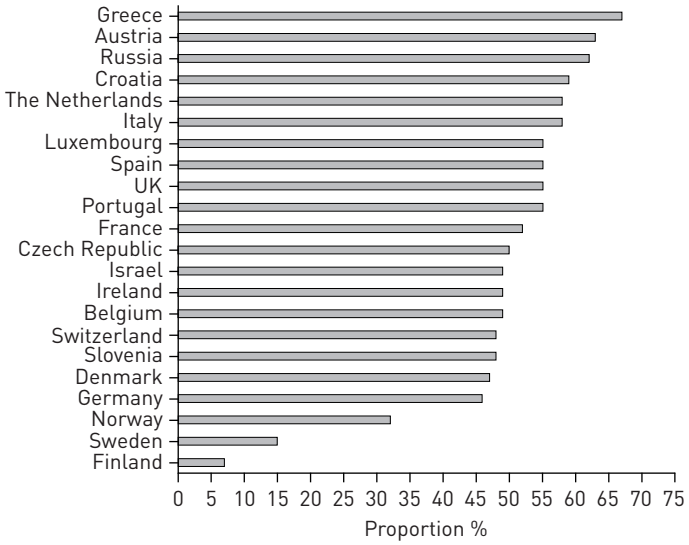

Figure 3. Proportion of children (⩽15 years of age) regularly exposed to second-hand smoke in a selection of European countries. Data from [40].

relatively common among secondary school pupils: 12% reported that smoking was allowed in their family car and 35% that they travelled in a car where smoking was allowed at least sometimes [50].

A recent study found that 19.3% and 10.0% of eastern and western European mothers, respectively, smoked in the vicinity of their children [51]. An Indian survey reported that 16.5% of students were exposed to SHS at home and 39.9% outside [52]. In addition, a German study showed adverse economic consequences of SHS exposure in children who are not only exposed to smoke indoors but also when parents reported exclusively smoking on a patio or balcony [53].

Impact of smoking exposure regulation across Europe

A limited number of EU member states are taking action against smoking in private places. Cyprus is the only member state at this stage that has prohibited smoking in cars in the presence of children under 16 years of age and Ireland, the first member state to introduce a comprehensive ban on smoking in public places, is working in this direction [54].

The UK smoke-free legislation prohibited smoking in enclosed public places, workplaces and work vehicles without covering private dwellings and private vehicles. However, no published, peer-reviewed evidence has shown an increase in smoking in the home after the smoke-free legislation adoption. On the contrary, overall levels of SHS exposure among UK children has fallen substantially. In fact, in England, the proportion of smoking parents adopting smoke-free home policies has risen from 16% in 1998 to 48% in 2008 [47].

Evidence suggest that where work and public places are smoke free, parents are more likely to make their own home a tobacco-free zone. Furthermore, smoke-free workplaces encourage smokers to quit. The reduction in smoking among adults means that fewer children are likely to be exposed to smoke at home [47, 55].

The extent to which smoking is banned across EU member states varies considerably between the countries. The legislation has been moving towards stricter control or a total ban of smoking in public places, which is confirmed by a 14% decrease in SHS exposure in drinking and eating places in the period 2009–2012. Figure 4 shows that the largest decrease in SHS exposure in public settings was observed in Spain (about -70%) due to one of the stricter antismoking regulations in the EU, introduced in 2011. Large decrements are also observed in Belgium, the Netherlands and Poland. Despite a general positive support by the majority of EU citizens towards tobacco control measures (76%), eight countries report an increment of exposure, Greece shows the highest change (about +13%) due to a weak implementation of the regulation [8]. As expected, nonsmokers show higher levels of support for all measures than smokers [8].

When smoke-free legislation is strictly enforced, a consistent improvement in air quality and reduction in the levels of indoor $PM_{2.5}$ have been reported [56, 57].

Positive health impacts, in terms of reduction of cardiorespiratory morbidity, have appeared very quickly after the implementation of smoke-free legislation. Reductions in acute coronary events [58], and cardiovascular, cerebrovascular and respiratory mortality [59], preterm births, and hospital attendance for childhood asthma [60] were found after the smoking ban.

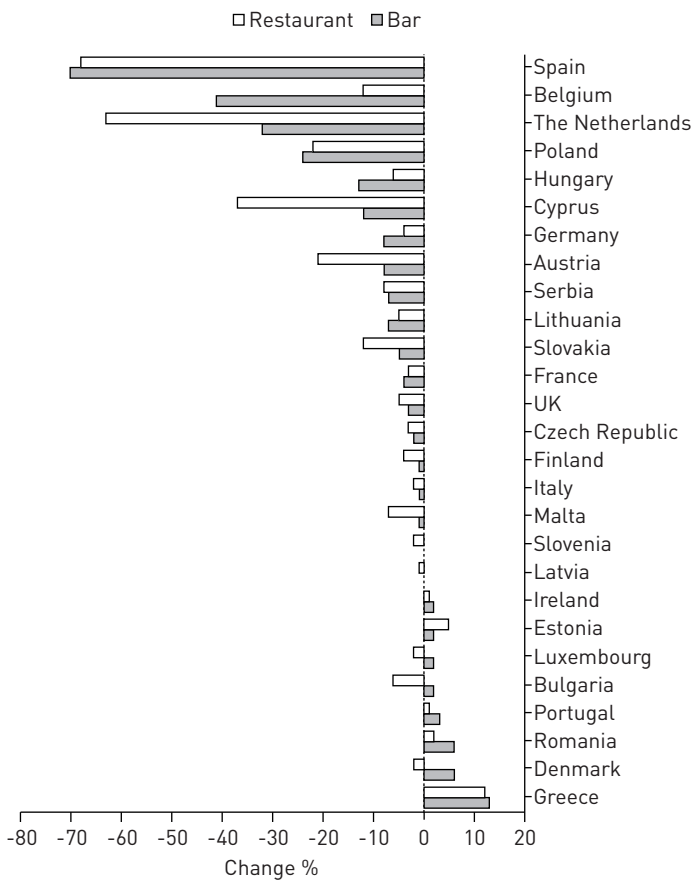

Figure 4. Per cent change of exposure to tobacco smoke, from 2009 to 2012, in public settings of the 27 European Union member states. Data from [8].

The economic impact of smoking bans on the restaurant/hospitality sector is limited (neutral or even positive) [56]. Positive impacts include the improved health of employees in terms of improved respiratory health [54].

Conclusion

Smoking still represents a relevant public health issue. Despite the progress in fighting the tobacco epidemic, the worldwide data on the prevalence and absolute number of smokers call for us to address tobacco control policies better.

In Europe, considerable differences in smoking prevalence among and within countries reflect regional, social and political variations; the presence of some methodological problems in the collection of smoking data underlie the need for standardised surveys.

Millions of children suffer the harmful effects of SHS. An increasing number of countries have recently issued laws to regulate smoking in public places, but homes remain an unrestrained site where children are dangerously exposed to SHS.

Research on the relationship between active smoking and health is still in progress, including questions over the role of smoking in the natural history and individual susceptibility of some (respiratory and nonrespiratory) diseases. Further investigations are needed to study the health effects of SHS and THS relevant to different exposure pathways and profiles. It is also very important to evaluate how THS may affect the lung development through the *in utero* exposure during the pre-natal life.

EU policy-makers should continue to enhance smoke-free laws with supporting advocacy measures, such as protecting children and increasing resources to give up tobacco use. Cooperation at the EU level by setting up a network of national focal points for tobacco control is also advisable. Pulmonary physicians are at the frontier of the smoking epidemic [61].

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Chapter 14

Outdoor air pollution

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The effects of air pollution on health became evident after episodes of extraordinarily high levels of airborne pollutants in the 1930s. Thereafter, research addressed the health effects of current levels of outdoor air pollution, which made it possible to implement monitoring of air pollutants and policies to reduce the impact on health. Worldwide, studies have assessed an increase in mortality, mainly due to respiratory and cardiovascular diseases, associated with long- and short-term exposure to air pollutants (especially particulate matter). Evidence of the effects on morbidity is increasing. The findings clearly indicate the need to reduce population exposure to air pollutants in order to protect human health. Some scientific issues related to exposure assessment and biological mechanisms of damage remain unaddressed. We provide a brief synthesis of the current knowledge of the effects of particulate matter, with specific attention given to the most innovative contributions.

The health effects of air pollution have been well known for many years, due to the serious epidemics of mortality and respiratory morbidity associated with episodes of very high air pollution in the 1930s and in the 1950s [1–5]. Thereafter, the research community focused on the possible health effects related to the current, lower levels of outdoor air pollutants. The results of more than a decade of epidemiological studies starting in the 1990s [6–9] provided an important contribution to the development of air quality standards in the USA [10] and the global World Health Organization (WHO) air quality guidelines [11, 12]. The most recently updated national standards for air pollutants were issued by the US Environmental Protection Agency in 2012 [13], while the European Directive on air quality [14] is still under revision. Table 1 reports the air quality standards adopted in different countries compared with the air quality guidelines recommended by WHO.

A health impact assessment of air pollution and the possible health benefits of interventions to reduce air pollution has been performed for several European cities [15]. In addition, accountability studies have addressed the chain of responsibility from the pollution source to population exposure, detailing all steps at which remedial actions can be introduced [16]. Accountability studies include city-wide interventions, such as the congestion charge adopted in London, UK, to reduce traffic pollution [17], and national plans to reduce emissions [18].

Additional epidemiological studies on the health effects of air pollution have been performed over the past decade using more accurate methods to assess exposure (air pollution

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Table 1. Comparison of World Health Organization (WHO) guidelines and standards from different countries

Source	Selected air quality guidelines and standards									
	PM_{10} μg·m^{-3}		$PM_{2.5}$ μg·m^{-3}		NO_2 μg·m^{-3}		SO_2 μg·m^{-3}		O_3 μg·m^{-3}	
	1 year	24 h	1 year	24 h	1 year	24 h	1 year	24 h	1 year	8 h
WHO (2008–2010)	20	50	10	25	40	200		20		100
European Union (2006)	40	50	25		40	200		125		120
USA (2012)	50	150	12	35	100[#]	188		197[¶]		150
California	20	50	15	65						
Brazil	50	150								
Mexico	50	120	15	65						
South Africa	60	180	15	65						
China (2012), urban and industrial areas	70	150	35	75	40	80	60	150		160

PM_{10}: particulate matter with a diameter <10 μm; $PM_{2.5}$: particulate matter with a diameter <2.5 μm; NO_2: nitrogen dioxide; SO_2: sulfur dioxide; O_3: ozone. [#]: including primary and secondary NO_2; [¶]: in 1 h.

dispersion models, chemical transport models, land use regression models and source apportionment models) and to estimate the health effects (multi-city studies, multi-pollutant studies and cohort studies) contributing to our understanding of the causal relationship between exposure and health. Several reviews are already available [8, 9, 19–28] that allow evaluation of the magnitude of the main effects and an assessment of the heterogeneity across world areas and populations.

Herein, we provide a brief synthesis of the current knowledge on the effects of air pollution, giving specific attention to the most recent and innovative contributions on particulate matter, the most health-relevant pollutant in the atmosphere.

Exposure assessment to air pollution

Air pollution is a complex mixture that includes particulate matter, ozone, carbon monoxide, sulfur oxides, nitrogen oxides, volatile organic compounds (*e.g.* benzene, toluene and xylene) and several other gases. An air pollutant is any substance (natural or anthropogenic) that is present in the atmosphere and can pose a threat to human health because of its high concentration or its intrinsic toxicity. Air pollutants derive from various natural and anthropogenic sources. Pollutants can be either directly emitted into the air (primary pollutants) or can be formed in the atmosphere from gaseous precursors such as SO_2, NO_2 and volatile organic compounds (secondary pollutants).

The chemical composition of air pollution shows both spatial and temporal variations that reflect local sources and long-distance transport, and is influenced by meteorological conditions, including sunlight intensity.

Due to its physical and toxicological characteristics, particulate matter is the most health-relevant pollutant in the atmosphere [29]. Particulate matter is composed of a mixture of solid and liquid particles of different size, origin and composition. Inhalable particulate matter has a diameter <10 μm (PM_{10}), ranging from 0.01 μm to 10 μm. They are deposited differentially within the upper airways (nasopharynx and larynx), conducting airways and

alveolar region depending upon their aerodynamic size, airway anatomy and ventilation pattern. PM_{10} includes two size fractions. 1) Coarse particles with an aerodynamic diameter >2.5 μm, mostly from natural crustal sources (soil, volcano and wildfires) including silicates, oxides of aluminium, iron, calcium and potassium, but also heavy metals from metallurgic industries and organic carbon products from road re-suspensions, as well as pollens, endotoxins and other biological material. 2) Fine particles with a diameter <2.5 μm ($PM_{2.5}$), mostly from anthropogenic combustion processes (vehicles, industry, electric power and home heating systems) include sulfates, nitrates, metals, and above all, combustion products (elemental carbon and organic carbon). Ultrafine particles with a diameter <0.1 μm are the smallest of the fine particles; they also originate from combustion processes, but are characterised by different metal and polycyclic aromatic hydrocarbon compositions and by higher oxidative and toxic potential than fine particles [30–32].

The concentration of air pollutants in the outdoor environment is the most frequently used parameter to assess population exposure. Continuous monitoring is in place in several countries for major air pollutants including PM_{10}, $PM_{2.5}$, NO_2, SO_2 and O_3 [12], and for tracers of specific emissions such as cadmium, lead, mercury and polycyclic aromatic hydrocarbon [33]. Pollutant concentrations are currently measured using fixed monitors and allow both daily changes (used to assess short-term exposure related to acute effects) and annual mean concentrations (used to assess long-term exposure related to chronic effects) to be estimated. When monitors are adequately distributed throughout a city to cover enough areas, it becomes possible to estimate the spatial differences for long-term exposure and chronic health effects.

Air pollution models are also used to better assess spatial variability, which is useful for exposure assessment. We can distinguish the models as follows.

1) Dispersion models were the first instruments developed to predict air pollutant concentrations on various spatial scales. They use emissions and weather data, have moderate spatial resolution but poor temporal resolution, and usually do not estimate secondary pollution [34].

2) Chemical transport models use emissions, weather and chemistry data to fit dispersion, and physical–chemical transformations to capture secondary pollution. They have good time resolution and fair spatial resolution. The main limitation is the poor temporal resolution of emission data [35].

3) Land use regression models use air pollution data from dedicated monitors (often passive samplers) together with data about human activities, such as goods and power production, traffic, population density and weather. These models have good spatial resolution but poor temporal resolution [36].

4) Remote sensing models (aerosol optical depth) use direct satellite measurements of aerosols each day at all locations. These estimates have good temporal resolution and fair spatial resolution; however, their correlation with monitors varies temporally and the estimates may be limited by some weather conditions and cloud cover [37].

Source apportionment techniques are useful to identify the relevant sources of air pollution. The fundamental principle is that the mass of the pollutants in the atmosphere can be assumed to be stable; therefore, a mass balance analysis is used to apportion sources of airborne particulate matter. If the number, nature and quantitative emissions of the sources

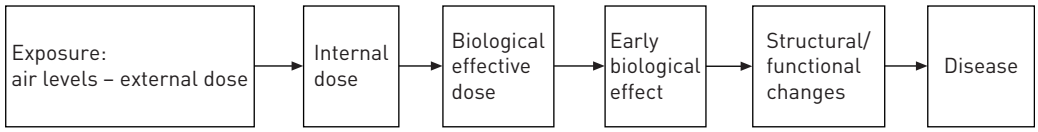

Figure 1. Biomarkers along the exposure–outcome chain. Reproduced and modified from [42] with permission from the publisher.

are known, only the mass contribution of each source has to be estimated. In contrast, if (as is more frequent) the source emissions are known only qualitatively, then factor analysis methods are applied to identify and quantify the sources of the air pollution [38, 39].

Bio-monitoring of exposure has recently been adopted to assess outdoor exposure to air pollutants and may have interesting developments that could provide a better understanding of the relationship between outdoor concentrations and individual exposure. Biomarkers of exposure directly measure the pollutants in the body fluids or tissues (internal dose), as is the case for polycyclic aromatic hydrocarbon [40], and indirectly measure their active derivative products (biological effective dose), as is the case in protein adducts of benzo[a]pyrene in human tissues [41], as they develop in the chain of steps linking exposure and disease (fig. 1) [42].

Air pollutants and health effects

The health effects of air pollutants were extensively reviewed by WHO in 2006 [12] and 2013 [27]. Specifically, acute health effects of air pollution included the progression of cardiovascular and respiratory diseases, acute respiratory infections, attacks of bronchial asthma, cardiovascular and ischaemic symptoms, and natural or cause-specific mortality. Chronic effects include respiratory symptoms, lung function reduction, chronic bronchitis, lung cancer and reduction of life expectancy.

Important statements regarding the toxic role of air pollution have been provided by scientific medical societies. In 2000, the American Thoracic Society recognised the effects of environmental pollutants and clarified the differences between acute and chronic effects as those observed in response to short-term (hourly or daily) changes of pollutant levels and those resulting in a reduced life expectancy from long-term exposure [43]. In 2004, the American Heart Association recognised the probability of cardiovascular events being linked to particulate matter [44], provided interesting insights towards understanding the mechanisms of the effects, and concluded that "the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality" [45]. In 2012, the international group investigating the Global Burden of Diseases [46] recognised the role of air pollution as one of the most important risk factors worldwide. Finally, in 2013, the International Agency for Research on Cancer classified outdoor air pollution and particulate matter as carcinogenic to humans (Group 1) [47].

Mechanisms of damage

It is recognised that the main mechanisms by which particulate matter induces health damage are oxidative stress at the cellular level and inflammation. C-reactive protein (CRP), an important acute-phase reactant with pro-inflammatory properties, has been indicated as a biomarker of the early biological effect due to particulate matter exposure (fig. 1). CRP is used for clinical purposes as an indicator of the presence and intensity of inflammation, while

experimental studies suggest that CRP levels increase in response to particulate matter exposure and elevated CRP levels have been found in children and healthy adults exposed to particulate matter [48]. However, epidemiological studies are not consistent with this evidence: long-term high residential exposure to $PM_{2.5}$ has been associated with increased CRP levels only in males [49]. CRP has been reported to increase in male patients with coronary health disease after ultrafine particle or PM_{10} exposures [50]. In contrast, particulate matter did not induce CRP increases in adults with chronic inflammatory conditions and CRP levels are not predictive of changes in FEV_1 or FVC over time [51]. Despite the difficulties of these studies, interest in bio-monitoring is increasing thanks to recent scientific evidence of changes in epigenetic markers, such as DNA methylation, as mediators between environmental exposure and health damage [52, 53].

Other mechanisms of disease pathogenesis operate at organ or system levels; thus, the study of the functional changes associated with air pollution exposure improves our knowledge about respiratory and cardiovascular impairment caused by air pollution. A few years ago, McCreanor *et al.* [54] reported a quasi-experimental study to confirm that adults with pre-existing respiratory disease, like asthma, may be at increased risk of a reduction in FEV_1 and FVC when exposed to diesel traffic (an indicator highly related to fine particles) compared to walking in a city park. More recently, Rice *et al.* [55] showed that lung function in a sample of the general population of the Framingham Heart Study cohort (offspring and third generation) were affected by previous-day exposure to moderate $PM_{2.5}$ levels (12 to 35.4 $\mu g \cdot m^{-3}$) compared to levels <12 $\mu g \cdot m^{-3}$ with a FEV_1 decrease of 20.1 mL (95% CI 33.4–6.9 mL) and a FVC decrease of 20.4 mL (95% CI 36.2–4.5 mL). The authors concluded that the general population, not just those who are sensitive, experience respiratory effects from ambient pollution at levels considered safe [55]. The pathways between the airway injury activation (with the increase of IL-6 and IL-8) and cardiac diseases have been specifically identified for coronary events [50]. Exposure to fine particles was associated with a mean $\pm$ SE 1.9 ± 0.7 beats$\cdot min^{-1}$ reduction in heart rate for 12 $\mu g \cdot m^{-3}$ of $PM_{2.5}$ and a reduced time interval between consecutive normal beats, equal to 4.2 ± 1.3 ms, for 4 h of $PM_{2.5}$ exposure. Both of these changes are clear predictors of mortality [56, 57].

Epidemiological aspects

A few methodological aspects deserve consideration when evaluating the epidemiological relationship between air pollution and health.

Time-series and case-crossover are the study designs most commonly used to evaluate the effects of short-term exposure on mortality and morbidity, while cohort (follow-up) studies are the preferred design to evaluate long-term effects. The degrees of the association between pollutants and health are expressed as relative risk (or hazard ratio or odds ratios according to the study design), but are more frequently reported as percentage increases in health risk for a specific increase in air pollutant level. The increase is expressed as a fixed increment (usually 10 $\mu g \cdot m^{-3}$) or as an increment equal to the IQR of the distribution of daily pollutant concentrations when short-term exposure (acute effects) are studied, or annual mean concentrations when long-term exposure (chronic effects) are studied. The fixed increment is more suitable to compare effects of the same pollutants in different times or across different areas; while the IQR increment allows the effects of different pollutants in the same time or space to be compared, since it takes into account the relative distribution characteristics of each pollutant.

One aspect that is often overlooked is the role of confounding and effect modification factors. In short-term studies, when the effects of daily changes of pollutants are evaluated, the relevant confounders are those associated with time, such as seasonality, meteorological factors or other pollutants, whereas personal or behavioural characteristics are unlikely to be confounders as they do not change day by day. In contrast, in long-term studies, when spatial differences in long-term exposure are relevant, proper control of behavioural and socio-demographic factors is important as these factors may be associated with exposure and health outcomes.

Effect modification refers to the possibility that some factors modify the main relationship between the pollutant exposure and health outcome; this is true when the association estimates differ significantly across the categories of the effect modifier. Some environmental factors such as other pollutants and seasonality, as well as some individual factors of susceptibility, could modify the effects of air pollution [58].

The "concentration–response function" describes the relationship between a pollutant and a specific health effect, *i.e.* the quantitative relationship between an increase of exposure level and the relative frequency of a given effect. The concentration–response coefficients may be used to predict the effects of changing concentrations of air pollutants in different scenarios and in cost-benefit analyses [59]. Until recently, the main assumption was that the relationship for most gases (NO_2 CO and O_3), and for PM_{10} and $PM_{2.5}$ (at concentrations $\leqslant 80$ $\mu g \cdot m^{-3}$) is linear [60]. A recent study aimed to predict worldwide relative risk functions [61]. It proposed a new approach to overcome the impact that random error of exposure measurements has on the relationship between particulate matter and cause-specific mortality, which causes a steeper concentration–response relationship at lower air pollution levels [61].

Health effects of short-term exposure to particulate matter

The multi-city studies carried out in the 2000s on the mortality and morbidity effects of short-term exposure to particulate matter have historical importance. Table 2 summarises the results of the APHEA (Air Pollution on Health: a European Approach) study in Europe [62–65], the NMMAPS (National Morbidity and Mortality Air Pollution Study) study in the USA [66, 67] and the APHENA (Air pollution and health: a European and North American approach) [68] study, combining data from Europe and North America to estimate the health effects of PM_{10} and $PM_{2.5}$. In the table, the more recent multi-city studies from Asia [25, 69, 70] and South America [71] are also included to provide a worldwide picture of the geographical differences. Three aspects emerge about short-term PM_{10}-related data. 1) Mortality increases have been observed everywhere but were lower in the USA than in Europe or China, and the strongest associations were found in countries with emerging economies, such as Latin America and South-East Asia. 2) The overall effect was generally larger for respiratory mortality than cardiovascular mortality, while the effects on hospitalisations for specific diseases, such as asthma in children and heart failure in adults, were particularly high. 3) The elderly are at higher risk of dying than other age groups both in North America and Europe.

Few results about the effects of $PM_{2.5}$ are available from these studies. However, fine particles represent the majority of PM_{10}, up to 70% in the whole year, both in winter (up to 85%) and summer (up to 65%) [60]. There is a great variability in the $PM_{2.5}/PM_{10}$ ratios due to the local sources (the average estimate of 65% in Europe has a range of 40% to 80%) [59], but the fine fraction seems to be the most damaging to health. Thus, to provide a larger picture of the $PM_{2.5}$ effects, we also considered the results from multi-city studies [72–74], two reviews

Table 2. Short-term effects of PM_{10} and $PM_{2.5}$ on mortality and hospitalisations from worldwide multi-city studies in 1997 to 2013

Study	First author [ref.]	Year	Locations	Time period	PM_{10}			$PM_{2.5}$		
					Exposure and age group	Mortality increase %	Hospitalisation increase %	Exposure and age group	Mortality increase %	Hospitalisation increase %
APHEA	Katsouyanni [62]	1997	12 cities in Europe	1975–1992	50 $\mu g \cdot m^{-3}$	Natural 2.2 (1.3–3.1)		Black smoke 50 $\mu g \cdot m^{-3}$	Natural 1.3 (0.8–1.7)	
APHEA2	Atkinson [65]	2001	8 cities in Europe	1988–1997	10 $\mu g \cdot m^{-3}$			Black smoke 10 $\mu g \cdot m^{-3}$		
APHEA2	Aga [63]	2003	29 cities in Europe		10 $\mu g \cdot m^{-3}$	Natural 0.67 (0.47–0.87)		Black smoke 10 $\mu g \cdot m^{-3}$	Natural 0.58 (0.32–0.84)	
					>65 years	Natural 0.74 (0.52–0.95)		>65 years	Natural 0.68 (0.43–0.92)	
APHEA2	Analitis [64]	2006	29 cities in Europe	1990–1997	10 $\mu g \cdot m^{-3}$	CV 0.76 (0.47–1.05)		Black smoke 10 $\mu g \cdot m^{-3}$	CV 0.62 (0.35–0.90)	
						Respiratory 0.71 (0.22–1.20)			Respiratory 0.84 (0.11–1.57)	
					0–14 years		Asthma 1.2 (0.2–2.3)	0–14 years		Asthma 1.3 (0.3–2.4)
					>65 years		COPD 1.0 (0.4–1.5)	>65 years		COPD 0.2 (-0.7–1.1)
NMMAPS	Dominici [66]	2005	90 cities in USA	1997–2000	10 $\mu g \cdot m^{-3}$	Natural 0.21 (0.09–0.21)				
NMMAPS	Dominici [67]	2006	90 cities in USA	1999–2002	10 $\mu g \cdot m^{-3}$		Heart failure 1.28 (0.78–1.78)			
					>65 years		Respiratory infections 0.92 (0.41–1.43) COPD 0.91 (0.18–1.64) Cerebrovascular diseases 0.81 (0.30–1.32)			
APHENA	Samoli [68]	2008	90 cities in USA		10 $\mu g \cdot m^{-3}$	Natural 0.29 (0.18–0.40)				
					>74 years	Natural 0.47 (0.31–0.63)				
			32 cities in Europe			Natural 0.33 (0.22–0.44)				
					>74 years	Natural 0.44 (0.29–0.58)				
			12 cities in Canada			Natural 0.84 (0.30–1.40)				
					>74 years	Natural 1.00 (0.25–1.80)				
PAPA	Wong [69]	2008	4 cities in Asia (south east coast)	1996–2004	10 $\mu g \cdot m^{-3}$	Natural 0.55 (0.26–0.85)				
						CV 0.58 (0.22–0.93)				
						Respiratory 0.62 (0.22–1.02)				
ESCALA	Romieu [71]	2012	9 cities in Latin America	1997–2005	10 $\mu g \cdot m^{-3}$	Natural 0.77 (0.60–1.00)				
						CV 0.72 (0.54–0.89)				
						Respiratory 1.39 (0.98–1.81)				

Table 2. Continued

Study	First author [ref.]	Year	Locations	Time period	PM_{10}			$PM_{2.5}$		
					Exposure and age group	Mortality increase %	Hospitalisation increase %	Exposure and age group	Mortality increase %	Hospitalisation increase %
Multi-city study	SHANG [25]	2013	33 studies in China					10 $\mu g \cdot m^{-3}$	Total 0.38 (0.31–0.45) CV 0.44 (0.33–0.54) Respiratory 0.51 (0.30–0.73)	
Multi-city study	LAI [70]	2013	23 cities in China	1993–2008	10 $\mu g \cdot m^{-3}$	Natural 0.31 (0.22–0.41) CV 0.49 (0.34–0.63) Respiratory 0.57 (0.40–0.75)				

Data are presented as % (95% CI). Time period and/or exposure columns are blank when information is lacking in the corresponding study. PM_{10}: particulate matter with a diameter <10 μm; $PM_{2.5}$: particulate matter with a diameter <2.5 μm; NMMAPS: National Morbidity and Mortality Air Pollution Study; APHEA: Air Pollution on Health: a European Approach; APHENA: Air pollution and health: a European and North American approach; PAPA: Public Health and Air Pollution in Asia; ESCALA: Multicity Study of Air Pollution and Mortality in Latin America; CV: cardiovascular.

[26, 28] and a few single-city studies [75–81]. What emerges from the $PM_{2.5}$-related data is as follows. 1) Effects of fine particles were less consistent than those of PM_{10} across studies, suggesting possible problems in exposure assessment or real differences in its composition across different areas. 2) Fine particles showed more important effects on mortality when compared to PM_{10}, thus indicating that they are more harmful for human health. 3) Short-term $PM_{2.5}$-related mortality from respiratory disease tends to be higher than cardiovascular mortality and the coefficient of hospitalisations for respiratory diseases is also much higher. 4) The effects on hospitalisations from cardiovascular disease are somewhat higher than effects on cardiovascular mortality, but a few cardiovascular causes of death (such as arrhythmias and stroke) have a large association with fine particles. The recent report for the WHO project HRAPIE (Health Risks of Air Pollution In Europe) [59] suggested the following concentration–response coefficients for the short-term effect of 10 $\mu g \cdot m^{-3}$ $PM_{2.5}$: mortality from all causes 1.23%; respiratory hospital admissions 1.9%; cardiovascular hospital admissions 0.9%.

The smallest fraction (diameter <0.1 μm) of the size distribution of particles is made up of ultrafine particles, mainly due to anthropogenic combustion. Ultrafine particles deal with a specific branch of toxicology, nanotoxicology [31]. Thus, several studies on ultrafine particles focus on their possible mechanisms of action, the most important are as follows. 1) Diffusion in all areas of the respiratory tract. 2) Translocation from lungs to blood and lymphatic circulation to reach sensitive tissues and organs such as bone marrow, lymph nodes, spleen and heart [30, 31]. Access to the central nervous system and ganglia *via* translocation along axons and dendrites has also been reported [82]. 3) Induction of a stronger inflammatory response to oxidative stress than larger particles, and pro-inflammatory effects both *in vivo* and *in vitro*. Strong inflammation from ultrafine particles has been related to their greater surface area compared to larger particles, and to the release of toxic free-radicals from their surface, which inhibit phagocytosis and cause cell injury known as oxidative stress. Common to other noxious exposures, oxidative stress works by depleting glutathione and generating ROS. The response to oxidative stress is organised in different steps: increasing glutathione production, activating transcription factors that lead to transcription of pro-inflammatory genes, increasing cytokines and other antioxidants that are active against oxidative stress [30, 31, 83].

There are several difficulties in estimating exposure to ultrafine particles and, as a consequence, it has been complicated to assess their possible effects. Moreover, many of the studied outcomes, such as lung function, heart rate variability and arrhythmias, were not consistently observed across the studies while no vascular impairment or effect on blood clotting were observed [27]. Some evidence of damage came from the European ULTRA study performed in Finland, the Netherlands and Germany, where ultrafine particles were associated with a decrease in PEF in both children and adults with asthma, and increasing asthma-like symptoms and medication use. Some specific effects were observed for respiratory (lag 1) and cardiovascular (lag 4) mortality [30]. The associations of ultrafine particles with mortality were not consistent across studies. However, the strongest association was with cardiovascular mortality [82]: the risk of out-of-hospital coronary deaths increased in Rome, Italy [84], stroke mortality increased in Helsinki, Finland [75], all-cause mortality increased (4.1%) in Erfurt, Germany [76], and cardiovascular mortality and hospitalisations increased in London [85]. Increases in hospitalisations for heart failure and COPD were reported in Rome in association with ultrafine concentrations [86].

Few epidemiological studies have explored the effects of all size fractions of particles. The assumption that coarse particulate matter (defined as particles with aerodynamic diameter

>2.5 $\mu g \cdot m^{-3}$ and <10 $\mu g \cdot m^{-3}$) is less harmful than fine particles, due to its mostly natural origin, has been reassessed [87]. In table 3, we report the results from multi-city studies that looked at fine, coarse and (less frequently) PM10 fractions. The relevant results are that the effects of coarse particles have been less frequently explored than other fractions, due to the negative results of the initial studies in North America [87, 88, 94] and London [95]; some contradictory results are available from studies that focused on Saharan dust in Europe [96–99]. The review on coarse and fine particles by BRUNEKREEF *et al.* [87] (not included as it does not provide pooled estimates) reported 12 studies of mortality and 14 studies of hospitalisations. Only four cities showed statistically significant increases in natural mortality associated with coarse particles, and the effects of fine particles were stronger than those of coarse particles everywhere apart from Mexico city, Mexico, and Vancouver, Canada. The US Environmental Protection Agency did not set standards for coarse particles in 2006 due to insufficient evidence linking short-term exposure and adverse health outcomes. However, in more recent studies, clearer effects of coarse particles (though of smaller magnitude than the effects of fine particles) emerged, particularly for respiratory mortality [89, 90, 100] and morbidity [91–93] in the USA and in Europe. It is noteworthy that the correlation between PM_{10} and $PM_{2.5}$ is high (Spearman correlation around 0.70), while the correlation between PM2.5 and coarse particles is lower (ranging from 0.25 to 0.70), which justifies studying the different fractions of PM10 in the same study. In addition, the measure of coarse particles is often an indirect measure calculated by subtracting a direct measure of PM2.5 from a direct measure of PM10, in which case, coarse particle measurement is affected by two measurement errors.

Chemical composition of particles

Recently, attention has being paid to the role of particle fraction size, their chemical components, and their sources. One seminal study from the USA showed that PM2.5 from mobile sources accounted for a 3.4% increase in daily mortality while fine particles from coal combustion sources accounted for a 1.1% increase. In contrast, crustal particles were not associated with daily mortality [101]. Particulate matter components were evaluated in this study to characterise the particulate matter fractions in order to determine their sources; this allows setting priorities for public interventions [102]. Additional studies followed relating chemical types and sources of particulate matter. Most of them had to set semi-continuous monitoring of chemical components such as metals, combustion products, secondary pollutants and organic compounds [103]. A large inter-comparison study [38] concluded that different methods of source apportionment were able to identify the same sources of PM2.5 and that effect estimates were not particularly influenced by these methods. However, while secondary sulfates were the most clearly identified components, traffic and wildfires sources were more affected by the different methods. The sources more frequently identified based on particulate matter components were soil, traffic, wood, oil, salts, incinerators, secondary SO_4 and secondary NO_3. Due to these methods, the high lung toxicity of PM2.5 was identified in cities were traffic and industries were more toxic [104]. Consistent associations between mortality and fuel combustion products (elemental carbon, organic carbon and NO_3) were found in California, USA, while mobile source-related emissions (Cu, Ti and Zn) exhibited the strongest associations with mortality [105]. PM2.5 from mobile sources and biomass (both forest and residential wood) combustion were associated with cardiovascular symptoms, while PM2.5 and secondary sulfates were associated with respiratory problems [39]. In Barcelona, Spain, traffic (vehicle exhaust, oil combustion and road dust), sulfates from shipping and construction dust were found to affect all-cause and cardiovascular mortality [106].

Table 3. Short-term effects of PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ on mortality and hospitalisations from multi-city studies in 1996 to 2013

First author [ref.]	Year	Study	Locations	Time period	PM_{10}		$PM_{10-2.5}$		$PM_{2.5}$	
					Exposure	Mortality increase %	Exposure	Mortality increase %	Exposure	Mortality increase %
Schwartz [88]	1996		6 cities in USA	1974–1991	10 $\mu g \cdot m^{-3}$		10 $\mu g \cdot m^{-3}$	Total (lag 0–1) 0.4% (0.1–1.0)	10 $\mu g \cdot m^{-3}$	Total (lag 0–1) 1.5% (1.1–1.9)
Zanobetti [89]	2009	Multi-city study	47 cities in USA	1999–2005			10 $\mu g \cdot m^{-3}$	Total (lag 0–1) 0.47% (0.21–0.73) CV (lag 0–1) 0.29% (-0.04–0.61) Respiratory (lag 0–1) 1.14% (0.43–1.85)	10 $\mu g \cdot m^{-3}$	Total (lag 0–1) 0.77% (0.43–1.12) CV (lag 0–1) 0.61% (0.05–1.17) Respiratory (lag 0–1) 1.63% (0.69–2.59)
Samoli [90]	2013	MED-PARTICLES	13 cities in Europe	2001–2010	10 $\mu g \cdot m^{-3}$	Natural (lag 0–1) 0.32% (0.13–0.52) CV (lag 0–5) 0.54% (0.09–0.99) Respiratory (lag 0–5) 1.12% (0.29–1.95)	10 $\mu g \cdot m^{-3}$	Natural (lag 0–5) 0.30% (-0.10–0.69) CV (lag 0–5) 0.33% (-0.78–1.46) Respiratory (lag 0–5) 0.76% (-0.70–2.25)	10 $\mu g \cdot m^{-3}$	Natural (lag 0–5) 0.55% (0.27–0.84) CV (lag 0–5) 0.86% (0.15–1.57) Respiratory (lag 0–5) 1.91% (0.71–3.12)

First author [ref.]	Year	Study	Locations	Time period	PM_{10}		$PM_{10-2.5}$		$PM_{2.5}$	
					Exposure	Hospital increase %	Exposure	Hospital increase %	Exposure	Hospital increase %
Host [91]	2008	Multi-city study	6 cities in France	2000–2003			10 $\mu g \cdot m^{-3}$	CV (lag 0–1) 0.5% (-1.2– 2.3)	10 $\mu g \cdot m^{-3}$	CV (lag 0–1) 0.9% (0.1–1.8)
							0–14 years	Respiratory (lag 0–1) 6.2% (0.4–12.3)	0–14 years	Respiratory (lag 0–1) 0.4% (-1.2–2.0)
							>64 years	Respiratory (lag 0–1) 1.9% (-1.9–5.9)	>64 years	Respiratory (lag 0–1) 0.5% (-2.0–3.0)
Peng [92]	2008	Multi-city study#	108 US counties	1999–2005			10 $\mu g \cdot m^{-3}$	CV (lag 0) 0.25% (-0.11–0.60)	10 $\mu g \cdot m^{-3}$	CV (lag 0) 0.71% (0.45–0.96)
							>64 years	Respiratory (lag 0) 0.26% (-0.32–0.84)	>64 years	Respiratory (lag 2) 0.44% (0.06–0.82)
Stafoggia [93]	2013	MED-PARTICLES	13 cities in Europe	2001–2010	14.4 $\mu g \cdot m^{-3}$	CV (lag 0–1) 0.53% (0.06–1.00) Respiratory (lag 0–5) 1.15% (0.21–2.11)	10 $\mu g \cdot m^{-3}$	CV (lag 0–1) 0.46% (0.10–0.82) Respiratory (lag 0–5) 1.24% (-0.32–2.82)	6.3 $\mu g \cdot m^{-3}$	CV (lag 0–1) 0.51% (0.12–0.90) Respiratory (lag 0–5) 1.36% (0.23–2.49)

Data are presented as % (95% CI), unless otherwise stated. PM_{10}: particulate matter with a diameter <10 μm; $PM_{10-2.5}$: particulate matter with a diameter ⩽10 μm and >2.5 μm; $PM_{2.5}$: particulate matter with a diameter <2.5 μm; lag: time in days between exposure and outcome; CV: cardiovascular. #: the values of coarse size fraction are adjusted for the fine fraction and *vice versa*.

Although many components have been found to contribute to the health effects of $PM_{2.5}$, in 2009, no evidence was available to identify which of them were more dangerous to health. LIPPMANN [107] called for more studies of health effects of particulate matter components. Hereafter, not much new evidence has emerged and the general conclusions remain the same [27]. However, two research reports from the Health Effect Institute provide interesting contributions. BELL *et al.* [108] assessed both mortality and morbidity associated with 52 chemical components of $PM_{2.5}$ in 187 US counties. VEDAL *et al.* [109] explored cardiovascular events and deaths associated with combustion products, metals and ions present in $PM_{2.5}$ in two on-going cohorts; the Multi-Ethnic Study of Atherosclerosis and the Women's Health Initiative in the USA [109]. Among single $PM_{2.5}$ components, ions (ammonium, nitrate and sulfate), black carbon (elemental carbon and organic carbon) and a few natural metals (Na and Si) made up $>$ 80% of the annual average $PM_{2.5}$ mass in the USA [107]. In terms of health effects, specific attention has been paid to carbonaceous products (elemental carbon and organic carbon) and toxic metals (As, Cd, Cr, Cu, Mn, Ni, Pb, Ti, V and Zn). Clear effects emerged for elemental carbon, nickel and vanadium. The two metals increased cardiovascular hospitalisations by 19% (95% CI 9.9–28) and 28% (95% CI 11–44), respectively, and respiratory hospitalisations by 223% (95% CI 37–410) and 392% (95% CI 46–738), respectively. Effects of elemental carbon were mostly explained by these two metals. In Europe, recent research suggests that BC and particles from combustion sources are more relevant to human health than particles from other sources [110].

Health effects of long-term exposure to particulate matter

Until recently, the scientific evidence on the health effects caused by long-term exposure to air pollutants was based on the results of two large studies conducted in the USA. The Six City study [6] and the American Cancer Society study [111] have shown an increased risk of death from cardiopulmonary causes and lung cancer in people living in cities with high levels of $PM_{2.5}$ compared to people living in less polluted cities. In 2009, an important study from the USA evaluated the effect of long-term exposure to both fine and coarse fractions of particulate matter on mortality among females in the Nurses' Health Study. An increased risk of mortality (HR 1.29, 95% CI 1.03–1.62) and fatal coronary heart diseases (HR 2.13, 95% CI 1.07–4.26) was associated with a 14 $\mu g \cdot m^{-3}$ increase in annual $PM_{2.5}$ concentrations, but no association was found with coarse particles (IQR 7.7 $\mu g \cdot m^{-3}$) [112].

The applicability of the results of these studies to those from Europe has been debated because of the differences in pollution sources and mixture of emissions in the USA and Europe (*e.g.* diesel vehicles account for only 2% of the total fleet in the USA whereas they are an important source of particulates in Europe).

Health effects from exposure to long-term air pollution have recently been studied in several European countries as part of the ESCAPE project (European Study of cohorts for Air Pollution Effects); a network of over 30 cohort studies across Europe with individual information on approximately 300 000 individuals. The most innovative aspect of ESCAPE is the method used for estimating exposure to air pollution. While in most of the previous studies average exposure in the city of residence was attributed to each subject, ESCAPE researchers estimate exposure of individuals at their residence. Land use regression models, based on intense monitoring campaigns and statistical modelling [113, 114], were able to predict particulate (PM_{10} and $PM_{2,5}$) and NO_2 at each residential address. These are pollutants primarily derived from vehicle traffic and heating systems.

Table 4. Association between exposure to PM_{10} and $PM_{2.5}$ and health events in adult population in Europe: ESCAPE project

Outcome	PM_{10} per 10 $\mu g \cdot m^{-3}$	$PM_{2.5}$ per 5 $\mu g \cdot m^{-3}$
Lung cancer incidence	1.22 (1.03–1.45)	1.18 (0.96–1.46)
Incidence of acute coronary events	1.12 (1.04–1.28)	1.13 (0.98–1.30)
Incidence of cerebrovascular events	1.11 (0.90–1.36)	1.19 (0.88–1.62)
Natural mortality	1.04 (1.00–1.09)	1.07 (1.02–1.13)
Mortality from cardiovascular diseases	1.02 (0.92–1.14)	0.99 (0.91–1.08)

Data are presented as relative risk (95% CI). ESCAPE: European Study of Cohorts for Air Pollution Effects; PM_{10}: particulate matter with a diameter <10 μm; $PM_{2.5}$: particulate matter with a diameter <2.5 μm.

The results of the European study have essentially confirmed those obtained in the North American studies. A significant association between chronic exposure to particulate matter (both $PM_{2.5}$ and PM_{10}) and incidence of acute coronary and cerebrovascular events, lung cancer and mortality due to non-accidental causes has been found. In particular, the study showed that for an annual increase of 10 $\mu g \cdot m^{-3}$ of PM_{10} the risk of developing lung cancer increased by 22% (table 4) [115], the risk of a first acute coronary event (myocardial infarction or unstable angina, both conditions mostly non-fatal) increased by 12% [116] and the risk of a cerebrovascular event (mostly non-fatal) increased by 11% [117].

The study also estimated that for an annual average increase in exposure of 5 $\mu g \cdot m^{-3}$ $PM_{2.5}$, There is an increased risk of death from non-traumatic causes of 7% [118]. The data analysis conducted in relation to specific causes of death did not show a significant association between pollutants and mortality from cardiovascular causes, although the study suggests an increased risk for mortality due to cerebrovascular events [119].

Table 5. Short- and long-term effects of $PM_{2.5}$ on hospitalisations assessed in the same population

Population	First author [ref.]	Hospitalisation increase %				
		All respiratory	CV	Stroke	Diabetes	Asthma
New England, USA: hospitalisations in >65-year-olds, 2000–2006	Kloog [120]					
Short-term $PM_{2.5}$ 10 $\mu g \cdot m^{-3}$		0.70 (0.35–0.52)	1.03 (0.69–0.45)	0.24 (-0.13–0.56)	0.96 (0.62–0.51)	
Long-term $PM_{2.5}$ 10 $\mu g \cdot m^{-3}$		4.22 (1.06–4.75)	3.12 (0.30–4.29)	3.49 (0.09–5.18)	6.33 (3.22–4.59)	
California, USA: hospitalisations in 0–18-year-olds, 2000–2008	Delfino [121]					
Low traffic levels, short-term $PM_{2.5}$ 11.1 $\mu g \cdot m^{-3}$						Cool season 6.11 (-0.68–13.36) Warm season 8.49 (-3.30–21.71)
High traffic levels, short-term $PM_{2.5}$ 11.1 $\mu g \cdot m^{-3}$						Cool season 10.86 (1.28–21.33) Warm season 10.62 (-5.85–29.96)

Data are presented as % (95% CI). $PM_{2.5}$: particulate matter with a diameter <2.5 μm; CV: cardiovascular.

Table 6. Evidence on health effects of long-term exposure to nitrogen dioxide and ozone

	Population	Mortality		
		Total	Cardiovascular	Respiratory
Nitrogen dioxide				
Beelen [119]	22 European cohorts (ESCAPE)	1.02 (0.99–1.04) per 10 μg·m^{-3}		
Hoek [24]	15 worldwide cohort studies	1.06 (1.03–1.08) per 10 μg·m^{-3}		
Faustini [123]	18 worldwide cohort studies	1.04 (1.02–1.06) per 10 μg·m^{-3}	1.13 (1.09–1.18)	1.02 (1.02–1.03)
Ozone				
Krewski [124]	ACS II cohort extended follow-up	1.02 (1.01–1.03) per 10 ppb		
Lipsett [125]	California Teachers Study, female cohort		1.09 (1.01–1.19) per 23 ppb	

Data are presented as relative risk (95% CI). ESCAPE: European Study of Cohorts for Air Pollution Effects; ACS: American Cancer Society; ppb: parts per billion.

In the ESCAPE results, the $PM_{2.5}$ effects on mortality were approximately twice as larger as the previous pooled estimates. In fact, a comprehensive meta-analysis of previous studies conducted worldwide [24] indicated that a 6% (95% CI 4–8%) increase in mortality for each 10 μg·m^{-3} increase in $PM_{2.5}$. The association in ESCAPE [118] persisted even among subjects with a residential $PM_{2.5}$ annual mean concentration <15 μg·m^{-3}. Also, for the study on incidence of coronary events, positive associations were also observed below the current annual European limit value for $PM_{2.5}$ and PM_{10} [116].

Studies evaluating both short- and long-term effects

Although the health effects of short- and long-term exposure to air pollutants have been studied separately, people experience both long- and the short-term exposure contemporaneously. The WHO REVIHAAP project (Review of Evidence on Health Aspects of Air Pollution) summarised the complex relationship of the two exposures: "while acute and long-term effects are partly interrelated, the long-term effects are not the sum of all short-term effects […] suggesting that effects are not just due to exacerbations, but may be also due to progression of underlying diseases" [27]. In this context, new approaches should give more attention to the complex interplay of the exposures.

Table 7. Evidence on health effects of short-term exposure to nitrogen dioxide and ozone

Nitrogen dioxide
New studies found associations between day-to-day variations in nitrogen dioxide and increases in mortality, hospital admissions and respiratory symptoms
Associations remain after adjustment for other pollutants (including PM_{10}, $PM_{2.5}$ and black smoke)
It is reasonable to infer that nitrogen dioxide has some direct effects
Ozone
Effects of daily ozone concentrations (maximum daily 1-h or 8-h mean) on all-cause, cardiovascular and respiratory mortality, as well as hospital admissions with cardiovascular and respiratory diseases emerged
Effects remain after adjustment for the effects of particles (PM_{10})

PM_{10}: particulate matter with a diameter <10 mm; $PM_{2.5}$: particulate matter with a diameter <2.5 mm. Summarised from [27].

Table 5 reports the results of two of these studies. The first assessed both short- and long-term exposure to $PM_{2.5}$ in the same population. The authors found a higher increase in hospitalisations related to long-term exposure compared to short-term exposure for both respiratory (4.22% *versus* 0.70%) and cardiovascular diseases (3.12% *versus* 1.03%) [120]. The second study explored the hypothesis that long-term exposure to high levels of pollutants, in addition to directly affecting human health, could also induce susceptibility to short-term exposure [122]. It found a higher increase in hospitalisations for asthma in people exposed to high traffic levels than in those exposed to low traffic levels, though the short-term daily exposure to $PM_{2.5}$ was the same, the long-term exposures in the two groups were different, both in the cool seasons (10.86% *versus* 6.11%, respectively) and in the warm seasons (10.62% *versus* 8.49%) [121].

To complete the picture of the health effects of outdoor air pollution, as assessed in the recent WHO REVIHAAP project [27], the evidence on health effects of long- and short-term NO_2 and in O_3 are presented in tables 6 and 7, respectively.

Conclusion

Air quality is a key environmental health determinant and the already strong scientific evidence on health effects has been further strengthened in recent years. Important improvements on exposure assessments make it possible to predict concentrations of the pollutants at the residential address and to better evaluate the effects of long-term exposures. Estimating health effects currently relies on well-based concentration–response functions and integrated efforts are ongoing to study a variety of health effects from various pollutants. Finally, new study designs can take into account combined effects of short- and long-term exposures and their complex interrelationship. From a public health perspective, the identification of health effects from exposure to $PM_{2.5}$ levels that are considered safe from the current legislation, calls for a prompt revision of the air quality standards currently in place in many parts of the world.

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Chapter 15

Indoor air pollution

Marzia Simoni[1], Isabella Annesi-Maesano[2,3] and Giovanni Viegi[1,4]

Daily activity requires individuals to spend as much as 90% of their time indoors. Some pollutants present in larger quantities indoors than outdoors, and with long-term exposure, even low concentrations of pollutants may have a significant biological impact. Indoor air pollution has been related to a higher risk of upper and lower respiratory tract irritation, respiratory and allergic symptoms and diseases, lung function reduction, BHR, and lung cancer.

Nearly half of the world's population uses biomass fuels for cooking, heating and/or lighting. Solid-fuel smoke causes huge health problems in developing countries but wood-burning populations in developed countries may also be at risk. According to the World Health Organization, 4.3 million people died from exposure to household air pollution (HAP) in 2012 (7.7% of the total annual global burden of disease). Globally, HAP ranks third among risk factors for DALYs. Air quality is particularly important for frail subpopulations (*i.e.* children, elderly people, and subjects with cardiorespiratory diseases or socioeconomic deprivation).

People spend most of their time in indoor environments, as much as 90% in industrialised countries, where air may be of poor quality and responsible for various adverse effects. Here, we report documented respiratory health effects of indoor air pollutants. For the purpose of this chapter, we have restricted our discussion in the following ways. First, risk factors covered in other chapters, like passive smoking and occupational exposures, are not covered. Second, the focus is on nonmalignant and noninfectious respiratory diseases. Last, the residential environment is mainly discussed, as this is the indoor environment where people spend most of their time by far.

The indoor environment

In the indoor environment, specific pollution sources may lead to high exposure with associated health risks. Indoor air quality (IAQ) is influenced by interaction between building characteristics and occupants. In addition, outdoor-generated pollutants may penetrate the indoor environment and contribute significantly to indoor exposure. Poor ventilation, as well as thermal insulation for reducing heat loss, may worsen IAQ. The levels of some pollutants

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may be 2–5-fold higher inside than outside buildings. Indeed, with long-term exposure, even low concentrations of indoor pollutants may have a significant biological impact [1].

Indoor exposure mainly occurs at home, at work and in schools, but also in day-care centres, social recreation settings or microenvironments (cars, buses, trains, subways, airplanes, *etc.*). The European Union (EU)-funded project THADE (Towards Healthy Air in Dwellings in Europe) showed that air pollution in dwellings is an important health problem [2]. The EU-funded European Federation of Allergy and Airways Diseases Patients Associations project on indoor air pollution (IAP) in schools pointed out that the right to breathe good air at school is largely ignored in many countries [3].

IAQ is particularly important for frail subpopulations, such as children, elderly people, and subjects with cardiorespiratory diseases or socioeconomic deprivation [4]. Children inhale a larger volume of air per body weight than adults and their defence mechanisms are still developing. Furthermore, humans become more vulnerable to environmental chemicals with ageing due to the deterioration of physiological and psychological processes [5].

Indoor pollutants and health effects

The EU Scientific Committee on Health and Environmental Risks reports that more than 900 different compounds can be detected indoors [6]. Most indoor pollutants derive from anthropogenic activity (table 1). Carbon dioxide is a by-product of human respiration and may worsen IAQ in crowded indoor environments with inadequate air exchange. Allergens, as well as infectious agents, also play an important role in IAP.

The 2010 Global Burden of Disease study reported that household air pollution (HAP) dropped by 37% between 1990 and 2010. Nevertheless, it ranks as the third risk factor for DALYs, *i.e.* the number of life years lost as a result of both premature death and disability [7].

Table 1. Main indoor pollutants and related sources

Source	Pollutants
Anthropogenic pollutants	
Combustion	
Unvented gas/kerosene heaters	CO, CO_2, NO_2, PAHs
Biomass (wood/coal) for heating cooking	CO, CO_2, PM, PAHs
Tobacco smoke	CO, CO_2, PM, VOCs, PAHs
New furniture, solvents, paint, adhesives, insulation, cleaning products, office supplies, synthetic building materials	VOCs, formaldehyde
Building materials, water sources	Radon
Allergens	
Dust, beds, carpets	Acarides (HDM)
Pets, birds, insects, rodents	Furs, hairs
Damp	Mould
Plants	Pollens
Viruses, bacteria	Biological contaminants

CO: carbon monoxide; CO_2: carbon dioxide; NO_2: nitrogen dioxide; PAH: polycyclic aromatic hydrocarbon; PM: particulate matter; VOC: volatile organic compound; HDM: house dust mite. Reproduced and modified from [1] with permission from the publisher.

Inhalation is the major pathway for air pollutants and there is large evidence that IAP affects respiratory health. We have previously evaluated the effects of indoor exposures not only by performing epidemiological studies but also through reviews of the literature on this topic [1, 8–10].

Several epidemiological studies point out that indoor factors might cause asthma in childhood. The most consistent findings for an association with asthma in childhood are related to exposure to environmental tobacco smoke (ETS), living in homes close to busy roads, pet-derived allergens, house dust mites and visible mould in the home [11]. A recent review, including studies on children under 5 years of age, indicates that exposure to IAP is significantly and consistently associated with severe acute LRTIs (OR 1.57, 95% CI 1.06–2.31, by meta-analysis) [12]. In adults, most studies on asthma and asthma-related symptoms strongly indicate adverse health effects of IAP, especially from fuel combustion, mould growth and ETS [13, 14]. IAP exposure is also positively related to increased risks of COPD and lung cancer [14]. There is increasing evidence of a relationship between indoor pollution and TB [15]. The commonest indoor risk factors and their related health effects are shown in table 2.

Particulate matter

Approximate estimates indicate that about 85% of all global particulate pollution occurs indoors [16]. A recent study performed in New York, NY, USA, residences of asthmatic children found that indoor sources accounted for about 72% of particulate matter with a 50% cut-off aerodynamic diameter of 2.5 μm ($PM_{2.5}$) [17]. Recent toxicological results highlight the importance of separating exposure into indoor- and outdoor-generated particles due to their different physicochemical and toxicological properties [18]. In indoor environments where people smoke, tobacco smoke is the major source of PM, accounting for up to 50–90% of the total indoor PM concentration. In low-income countries, one of the major sources of indoor PM is biomass fuel (wood, charcoal, dung, *etc.*), which is frequently burned in the home in open fires or inefficient stoves. In industrialised countries, most studies have focused on ETS as proxy of PM exposure and few have assessed the effects of measured indoor PM.

Table 2. Main respiratory health effects by common indoor pollutants

Pollutants	Effects
Combustion products, ETS (CO_x, NO_x, PM, wood/coal smoke)	Respiratory symptoms, lung function reduction, BHR, COPD, asthma
VOCs (alkanes, formaldehyde, esters, ketones)	Upper/lower respiratory tract irritation, asthma
Microorganisms (fungal spores, bacteria, viruses)	Respiratory infections
Allergens (pollens, moulds, mites, cockroaches, insects, dander, feathers)	Sensitisation (specific/total IgE), respiratory allergic diseases (asthma, rhinitis), hypersensitivity pneumonitis, chronic cough
Radon	Lung cancer

ETS: environmental tobacco smoke; CO_x: carbon oxides; NO_x: nitrogen oxides; PM: particulate matter; VOC: volatile organic compound. Reproduced and modified from [1] with permission from the publisher.

In children, indoor PM levels are associated with the risk of bronchitis-like symptoms, decreased lung function and asthma exacerbation: in asthmatic children, the risk of nocturnal symptoms and wheezing increased by 6% and 7%, respectively, for each 10-$\mu g \cdot m^{-3}$ increment in indoor $PM_{2.5}$ [13]. In France, increased prevalence of past-year asthma was found in schoolchildren exposed to high levels of $PM_{2.5}$ in classrooms (OR 1.21, 95% CI 1.05–1.39) [19]. Increased exposure to PM_{10} in classrooms was linked to higher risk of reduced nasal patency in schoolchildren in five European countries [20].

Findings in the general population are less conclusive: fewer studies found household exposure to PM to be a significant risk factor for respiratory symptoms [8, 9, 21].

Biomass fuel smoke

Nearly half of the world's population (>3 billion people) uses biomass fuels for cooking, heating and/or lighting [22]. Indoor solid-fuel smoke causes huge health problems in developing countries. However, wood-burning populations in developed countries may also be at risk from these exposures. Although the total percentage of people using solid fuel is decreasing, the absolute number is currently increasing [23]. Burning biomass fuels within the home in open fires or in inefficient stoves determines elevated concentrations of PM and carbon monoxide. 24-h indoor concentrations of PM_{10} generated from solid fuels in different settings are in the range of 300–3000 $\mu g \cdot m^{-3}$, with peaks as high as 20 000 $\mu g \cdot m^{-3}$ during cooking [23]. Biomass combustion is qualitatively similar to tobacco burning in terms of emissions of PM and gases. Moreover, particles from wood smoke are similar to those from traffic emission. Globally, in 2012, HAP from solid fuels is considered to be responsible for 7.7% of the total annual global burden of disease and for 4.3 million deaths yearly (mostly in low- and middle-income countries) [24]. Worldwide, HAP ranks first among the environmental risk factors for mortality [25].

Table 3 shows the results from systematic reviews and meta-analyses on the association between solid fuels use and health outcomes. There is consistent evidence for associations of solid fuel use with COPD and chronic bronchitis, with higher risk among females than males and from wood smoke than other fuels' smoke [26–28]. There is also evidence that biomass fuel use increases the risk of acute respiratory infections in children [28], mainly living in developing countries, but also in the USA and Italy [29]. Exposure to biomass fuel smoke also increases the risk of TB [23].

As concerns the effects on asthma symptoms and disease, results are inconsistent. Some studies found a significant relationship between asthma and the use of biomass fuels [30]. Conversely, a meta-analysis did not provide evidence of increased risk of asthma in children or females using biomass fuels [28]. In a recent study of 512 707 schoolchildren from 47 countries, the use of an open fire for cooking increased the risk of past-year wheeze in both children aged 6–7 years (OR 2.17, 95% CI 1.64–2.87) and adolescents aged 13–14 years (OR 1.35, 95% CI 1.11–1.64). However, in both age groups, no evidence of an association between the use of gas as a cooking fuel and either asthma symptoms or asthma diagnosis was found [31].

The International Agency for Research on Cancer (IARC) has classified the indoor combustion of coal emissions as Group 1, a known carcinogen to humans. Home exposure to coal combustion increases the risk of lung cancer, with strong evidence in females

Table 3. Pooled effects by exposure to biomass fuel smoke

Source	Outcome	Smoke	OR (95% CI)	RR (95% CI)
Kurmi *et al.* [26]	COPD	Solid fuels	2.8 (1.8–4.0)	
		Wood	4.3 (1.3–13.7)	
		Mixed biomass	2.5 (1.5–4.0)	
		Coal	1.8 (1.0–3.3)	
Torres-Duque *et al.* [27]	COPD in females	Solid fuels		3.2 (2.3–4.8)
		Biomass fuels	2.4 (1.5–3.9)	
Torres-Duque *et al.* [27]	COPD in males	Solid fuels		1.8 (1.0–3.2)
Kurmi *et al.* [26]	Chronic bronchitis	Solid fuels	2.3 (1.9–2.8)	
		Wood	2.6 (2.1–3.3)	
		Mixed biomass	2.5 (1.9–3.4)	
Kurmi *et al.* [23]	TB	Biomass fuels	1.5 (1.1–2.2)	
Torres-Duque *et al.* [27]	Acute LRTI[#]	Solid fuels		2.3 (1.9–2.7)
Po *et al.* [28]	ARI[#]	Biomass fuels	3.5 (1.9–6.4)	

RR: relative risk; ARI: acute respiratory infection. [#]: in children.

(relative risk (RR) 1.9, 95% CI 1.1–3.5) and moderate evidence in males (RR 1.5, 95% CI 1.0–2.1) [27].

Nitrogen dioxide

Indoor nitrogen dioxide is mainly generated by gas-fuelled cooking and heating appliances. Some studies have found adverse respiratory health effects from indoor nitrogen dioxide, whereas other studies have not. These conflicting results could be partially explained by the difficulty in determining exposure.

Longitudinal studies on asthmatic populations, mainly children, indicate associations between nitrogen dioxide concentration and respiratory symptoms (wheezing, breathing difficulty, chest tightness, shortness of breath and cough) [14]. Among asthmatic children living in urban environments, each 20-ppb increase in indoor nitrogen dioxide exposure is associated with a higher incidence of cough (incidence rate ratio (IRR) 1.10, 95% CI 1.02–1.18) and nocturnal symptoms (IRR 1.09, 95% CI 1.02–1.16) [32]. The results of a recent meta-analysis including 41 studies of children showed that gas cooking increases the risk of asthma (OR 1.32, 95% CI 1.18–1.48) and indoor nitrogen dioxide exposure increases the risk of current wheeze (OR for a 15-ppb increase 1.15, 95% CI 1.06–1.25) [33]. Interestingly, asthmatic children exposed to nitrogen dioxide indoors, even at levels well below the US Environmental Protection Agency (EPA) outdoor standard (53 ppb), are at risk of increased asthma morbidity [34].

Volatile organic compounds

Volatile organic compounds (VOCs) are important indoor air pollutants mainly produced by natural sources and anthropogenic activities (paints, wood, fabrics, cleaning agents, air fresheners, cosmetics, furnishings, floor/wall coverings, *etc.*). In western countries and westernised societies, computers and televisions also emit VOCs. Indoor VOC levels exceed

those found outdoors. The exposure to VOCs may be related to a spectrum of conditions ranging from irritations to very severe effects, including cancer. Many studies indicate that health effects are related to very low levels of exposure.

In a Japanese study of 425 households with 1479 residents, formaldehyde and other aldehydes were the main VOCs, and were related to increased risk of sick-building syndrome [35].

There is evidence of associations between increased residential VOC levels and respiratory symptoms/diseases [1, 36] but the results are inconsistent [37]. Residential VOCs, as well as emission-related materials or renovation/cleaning activities, have been related to higher risk of respiratory/allergic effects in infants and children (*i.e.* asthma, wheeze and bronchitis), reduced lung function, atopy and severity of sensitisation, rhinitis, and pulmonary infections [36]. The highest associations were for toluene with increased specific IgE levels (OR 11.2), for formaldehyde with bronchitis (OR 8.2), for paint with pulmonary infections (OR 5.6), and for plastics/plasticisers with persistent wheeze (OR 3.4); odds ratios for aromatic chemicals/phthalates with asthma diagnosis ranged from 1.2 to 2.9 [36].

In a Chinese survey of a large sample (n=31 049) of children (age 2–14 years), recent home renovation significantly increased the risk of cough, phlegm, current wheeze and doctor-diagnosed/current asthma [38]. Epidemiological studies report associations with some asthma-like symptoms and domestic paint exposure, especially in children. However, the epidemiological evidence is weak and insufficient to infer causality for asthma exacerbation in children and/or adults [39].

A French study evidenced a higher risk of breathlessness in those exposed to elevated concentrations of domestic toluene and xylene, which was significant in the elderly (OR 3.36, 95% CI 1.13–9.98 for toluene; OR 2.85, 95% CI 1.06–7.68 for xylene) [40]. High concentrations of VOCs in French homes were associated with increasing prevalence of asthma and rhinitis in adults [41]. There is a relationship between the urine concentration of *S*-phenylmercapturic acid (a biomarker of benzene exposure) and asthma, suggesting that home exposure to even low levels of benzene is a risk factor for childhood asthma [42].

A survey using personal assessment of VOC exposure in adults found an increased risk of doctor-diagnosed asthma among those exposed to aromatic compounds (OR 1.63, 95% CI 1.17–2.27) [43].

Formaldehyde is currently one of the mostly studied pollutants in indoor air. The IARC has classified formaldehyde in Group 1 (human carcinogen). Several studies showed an increased risk of asthma in children exposed to higher levels of formaldehyde, whereas others did not find any significant association [13]. Children exposed to 60 $\mu g \cdot m^{-3}$ formaldehyde had a 39% increased risk of asthma compared with less exposed children (<10 $\mu g \cdot m^{-3}$) [44]. In a meta-analysis, there was a 17% increase in the risk of asthma in children (pooled OR 1.17, 95% CI 1.01–1.36) for each 10-$\mu g \cdot m^{-3}$ unit increase in formaldehyde concentration [45]. Significant associations between formaldehyde levels and incidence of asthma have been found in nonatopic children [46]. Exposure to formaldehyde in classroom was related to rhinitis among schoolchildren. However, due to various limitations or to mixed exposures where the effects of formaldehyde are indistinguishable from those of other components, associations between exposure to formaldehyde in dwellings and development/exacerbation of asthma or sensitisation have yet to be confirmed [11, 47, 48].

It has been suggested that VOCs produced by microorganisms (mVOCs) such as moulds may contribute to asthma or asthma/chronic bronchitis-like symptoms [49]. However, the role played by mVOCs is still controversial due to their low specificity towards fungi and their very low concentrations in the indoor air.

Radon

Radon was the first environmental agent to be identified as a cause of lung cancer. Residential radon exposure is considered the second cause of lung cancer after tobacco smoking, playing a role in 30% of lung cancer deaths in never-smokers [50].

Exposure to over 148 $Bq \cdot m^{-3}$ radon (threshold proposed by the EPA) increases the risk of lung cancer by 34% (95% CI 7–68%) [51]. In never-smokers, the pooled excess risk of lung cancer from residential radon was 10.6% (95% CI 0.3–28%) in Europe, and 10% (0.91–42%) in the USA and Canada, per each 100-$Bq \cdot m^{-3}$ increase [52]. Consequently, the World Health Organization (WHO) issued recommendations of levels under 100 $Bq \cdot m^{-3}$ [50].

However, there may be no threshold in the linear dose–response relationship between indoor radon and lung cancer. In a recent case–control study performed in Spain, subjects exposed to 50–100 $Bq \cdot m^{-3}$ showed an odds ratio of 1.87 (95% CI 1.21–2.88) and those exposed to 148 $Bq \cdot m^{-3}$ or more had an odds ratio of 2.21 (95% CI 1.33–3.69) [53].

Allergens

Indoor allergens mainly originate from dust mites, domestic pets, cockroaches, pests and moulds. Allergen exposure is a known environmental risk factor associated with symptoms and severity of allergy. In adults, a lower prevalence of allergic sensitisation has been related to a lower indoor allergen exposure [54]. In the USA, 56% of asthma cases were attributable to atopy [55]. However, there is still debate on whether allergen avoidance prevents the onset of allergy or a direct causal relationship between exposure to allergen and asthma incidence exists [56, 57]. The exposure–response relationship between indoor allergens and respiratory/allergic conditions is complex, depending on several factors, such as genetic susceptibility or gene–environment interaction.

Mite allergens

Dermatophagoides pteronyssimus and *Dermatophagoides farinae* are the two most important sources of mite allergens. Longitudinal studies provide scarce evidence of a direct link between mite exposure and asthma onset. There is sufficient evidence of an association of mite allergen exposure with allergic sensitisation to mites (the major predictor for asthma) but preventive effects of mite allergen avoidance are not conclusive [11]. Observational studies show a causal relationship between levels of mite allergens and the development of asthma [11] but the results are not confirmed by randomised clinical trials in asthmatics [58]. However, the potential effect on the onset of specific allergic sensitisation and asthma by mite allergen exposure is clearer than that by other indoor factors [11].

Pet allergens

The assessment of the associations of pet allergen exposure and development of allergic sensitisation/symptoms only derives from observational studies, as it is difficult to perform randomised controlled trials. This is particularly true for the cat allergen Fel d1 because it is

distributed throughout the community (schools, homes, *etc.*), even those who do not live with a cat in their home may be exposed in other places.

In addition, effects of pet exposures are inconsistent. Some studies suggest that cat allergen is associated with the development of cat sensitisation, which is a strong risk factor for asthma; other studies suggest that cat ownership may have an inverse relationship with sensitisation, and early-childhood exposure might even be associated with lower rates of cat sensitisation in adulthood [59].

A review of epidemiological studies reports contradictory relationships between cat or dog exposure and asthma in children [60]. It seems that cat or dog exposure in early life is not related to the development of asthma or asthma symptoms. However, cat exposure during infancy increases the risk of cat sensitisation. Conversely, a similar dog exposure seems to protect children from the onset of sensitisation to inhalant allergens. In summary, this review shows that cat and dog avoidance cannot prevent allergy.

An Italian study of 20 016 children found that cat exposure in the first year of life was significantly associated with current wheezing (OR 1.88, 95% CI 1.33–2.68) and current asthma (OR 1.74, 95% CI 1.10–2.78) at the age of 7 years. No significant effect of dog exposure in the first year of life or later on respiratory/allergic symptoms was found [61].

In adults (n=6292; 20–44 years old), acquiring a cat during the follow-up period was associated with new-onset sensitisation (RR 1.85, 95% CI 1.23–2.78); conversely, ownership of cats during childhood was a significantly protective factor [62].

Fel d1 exposure in a home with a cat is far higher than the levels necessary to induce an allergic response. A significant number of atopic children and young adults living in homes with a cat do not report relevant symptoms. Recently, it was shown that tolerance associated with early exposure can be long-lived [63].

Damp, mould and derived products

Damp in the indoor environment is universally accepted as a major risk factor for health effects in people, especially children. Excess dampness facilitates the proliferation of moulds, cockroaches and mites. Moulds produce allergens, mVOCs and mycotoxins. Damp may also promote bacterial growth and the survival of viruses.

Visible damp and moulds are consistently associated with multiple allergic/respiratory effects in both allergic and nonallergic individuals [64].

In 2009, WHO published a review of epidemiological studies on damp and mould health effects [65]: damp and mould are associated with approximately 30–50% increases in respiratory and asthma-related health outcomes. Based on the results of a meta-analysis (table 4), WHO concluded that there is no sufficient epidemiological evidence for a causal relationship between indoor damp or mould and any specific human health effect; however, there is sufficient evidence of associations between indoor dampness-related factors and upper respiratory tract symptoms, cough and asthma exacerbations.

A recent meta-analysis provides new evidence that damp and moulds in the home increase the risk of rhinitis and its subcategories (table 4) [66]. Interestingly, in this study, the

Table 4. Pooled effects by exposure to damp or mould

Source	Outcome	Pooled OR (95% CI)	Pooled EE (95% CI)
WHO [65]	Current asthma	1.56 (1.30–1.86)	
	Ever diagnosed with asthma	1.37 (1.23–1.53)	
	Asthma onset	1.34 (0.86–2.10)	
	Wheeze	1.50 (1.38–1.64)	
	Cough	1.67 (1.49–1.86)	
	URTS	1.70 (1.44–2.00)	
Jaakkola *et al.* [66]	Rhinitis		2.18 (1.56–2.12)
	Allergic rhinitis		1.51 (1.39–1.64)
	Rhinoconjunctivitis		1.66 (1.27–2.18)

EE: effect estimate; WHO: World Health Organization; URTS: upper respiratory tract symptoms.

strongest association was found for mould odour with rhinitis (estimated effect 2.18, 95% CI 1.76–2.71) [66].

Other studies found significant effects of damp/mould exposure or related problems in both children and adults. A recent Chinese study including more than 13 000 children (4–6 years old), found the following associations: visible mould with asthma (OR 1.32, 95% CI 1.07–1.64), damp clothing and/or bedding with dry cough (OR 1.78, 95% CI 1.37–2.30), and condensation on windows with hay fever (OR 1.60, 95% CI 1.27–2.01). Moreover, early exposure to visible mould was related to higher risk of dry cough (OR 2.20, 95% CI 1.55–3.11) and rhinitis (OR 1.57, 95% CI 1.11–2.21) [67]. In over 5000 middle-aged Tasmanians, recent exposure to visible mould at home was associated with current asthma (OR 1.26, 95% CI 1.06–1.50), wheeze (OR 1.34, 95% CI 1.17–1.54) and nocturnal chest tightness (OR 1.30, 95% CI 1.12–1.51) [68].

The evidence for associations with directly measured exposures is less consistent. In children/infants or young adults, there is evidence of associations, although not always statistically significant, between the number of fungal colonies and the risk of allergic sensitisation, cough, asthma and asthma-like symptoms [69]. Methods based on objective measurements of mould markers (*e.g.* ergosterol; extracellular polysaccharides; components of the bacterial cell wall, such as β-glucans; mycotoxins; and mVOCs) have been developed. However, the associations between these biological agents and health effects are inconsistent. Some studies even found protective effects from early exposures [13]. In recent years, significant associations were found between exposure to specific fungal DNA at school and wheeze, dry cough at night, persistent cough, daytime breathlessness or asthma diagnosis [69, 70].

Endotoxins

Endotoxins are components of the outer membrane of various Gram-negative bacteria. Sources of endotoxins may be humidifiers, keeping pets or contact with livestock, or storage of food waste.

There is conflicting evidence on the associations between exposure to endotoxins and respiratory/allergic effects [47, 64]. Significant associations have been found with asthma and

wheezing in children/infants [13]. In adults, endotoxin exposure at home, as measured in dust, significantly increased the risk for asthma [71], whereas the mattress endotoxin level did not affect respiratory health [72]. The exposure to endotoxins was also related to asthma severity and morbidity [73]. High exposure to endotoxins was significantly associated with the risk of COPD, COPD-like symptoms, BHR and wheezing [13].

Even if several population-based studies have shown a protective effect on risk of wheezing, asthma and atopy in children exposed to high household endotoxin concentrations, there is no sufficient evidence of a potential protective effect of microorganisms on respiratory health [74].

IAQ in schools

IAQ in schools has received particular attention over the past several years, since children spend a consistent part of the day in school. IAP in schools is the product of the combined effect of physical, chemical and biological factors, with the level of ventilation in the environment. Bacteria, moulds, VOCs, particles and carbon dioxide are the most common pollutants found in schools [1], where there is generally poor IAQ. As mentioned, correlations have been found between the concentration of the pollutants inside the classrooms and the onset of health problems in schoolchildren, predominantly respiratory and allergic symptoms and diseases [19, 20, 69, 70, 75].

Conclusion

In view of the large fraction of our time spent indoors, indoor environments significantly contribute to total human exposure to air pollutants. Indoor pollution largely affects respiratory health worldwide, as shown by many recent epidemiological studies, literature reviews and meta-analyses. New evidence is needed on controversial health–environment relationships. For instance, more effort is needed to add information on possible effects of indoor PM and other very common indoor home pollutants, such as specific VOCs, fungi or microbiological agents, on respiratory health in the general population.

Although preventive action through educational programmes, research, and policy changes might reduce the negative effects of IAP on the respiratory health status and quality of life of the general population, especially susceptible individuals, this has not been sufficiently documented and evidence is not sufficient to recommend guidelines on precise avoidance measures. However, patient education about trigger prevention and the importance of good IAQ at home are essential.

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Chapter 16

Work-related respiratory diseases in the European Union

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Occupational respiratory diseases contribute considerably to the total burden of respiratory diseases. The occurrence of classical respiratory occupational diseases, such as pneumoconioses, which are related to mining and mineral processing industries, has declined in most countries because of exposure control and automation. However, these diseases are still being observed in the construction industry due to the use of mechanical hand tools. In general, the role of asthma and COPD has become more dominant over the past decades. Lung cancer and mesothelioma generally occur after an active working life, but occupational exposure clearly contributes to their occurrence. The burden of these diseases related to occupational exposures, and expressed in DALYs, are amongst the highest worldwide. The need to control exposure by setting standards for levels of pollutants in the work environment should continue to receive attention and priority.

As part of the Global Burden of Disease project, it was estimated that in 2005, 52 700 deaths were due to respiratory diseases resulting from occupational particulate exposure. Of these, 6200 were due to asthma, 39 300 were due to COPD and 7200 were due to pneumoconiosis. These numbers of deaths are associated with 868 000 DALYs: asthma 139 000 DALYs; COPD 468 000 DALYs; and pneumoconioses 261 000 DALYs [1]. More recent figures are not yet available from the Global Burden of Disease project, but these data illustrate the impact that occupational exposure has on disease burden in the general population.

Respiratory diseases are the third most prevalent occupational disease category in the European Union (EU) according to a survey of occupational diseases [2]. The prevalence of respiratory diseases was 296 per 100 000 population. The highest proportion was found in the mining industry. This amounts to almost 600 000 persons in the former 15 EU member states. Many of these diseases, although acquired while working, are chronic or occur after higher cumulative exposure, thus explaining the highest prevalence amongst older workers (0.5% aged 55–64 years).

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It is often thought that occupational diseases are specifically related to factors within the work environment. Pneumoconiosis and cancer (for example, mesothelioma) are examples of such diseases. Exposure within the work environment can also contribute to both the development and worsening of respiratory diseases, such as COPD, asthma and bronchopulmonary cancer. However, these diseases can also be caused by environmental or lifestyle factors, such as smoking. For diseases like asthma and COPD, which can be caused by multiple factors, reliable information on the contribution from occupational exposures can only come from well-designed epidemiological studies. A further complication is that occupational asthma is not diagnosed specifically in general population studies. An attributable risk has to be calculated, which is usually based on crude information about exposure and for a particular asthma phenotype. Based on such epidemiological analyses, it has been shown that the population attributable fraction of occupational factors in mortality from respiratory diseases is far from negligible [3]. Despite a substantial contribution at the population level to disease occurrence, it is often difficult to substantiate and document specific causes in individual subjects. Large epidemiological studies have also sought to determine the contribution of workplace exposure to common respiratory diseases, such as asthma [4, 5].

In several countries, pneumologists and/or occupational physicians have created systems for the voluntarily reporting of occupational respiratory diseases. SWORD (Surveillance of Work Related and Occupational Respiratory Disease), which was created in 1989 in the UK, is the most well known of these systems [6]. Although voluntary reporting systems have some weaknesses, they provide useful estimates on the involvement of workplace exposure in the occurrence of respiratory disease. In addition, the systems have helped identify priorities for prevention.

In this chapter, the major categories of respiratory disease will be reviewed and, where possible, we will discuss the contribution of occupational exposures to the prevalence of respiratory diseases. Two articles have recently been published on the same topic [7, 8]. Although we will only present a small amount of quantitative information in this chapter, our aim is to aid the identification of the main areas in which efforts are required in Europe for the prevention, diagnosis, management and compensation of workplace-induced respiratory diseases. We will also cover the areas of management and prevention.

Agents responsible for work-related diseases

Several different agents are associated with the occurrence of work-related respiratory diseases, ranging from (potentially fatal) acute inhalation incidents and inhalation fevers, through infections, asthma, COPD and interstitial lung disease (ILD) (including pneumoconiosis), to respiratory cancer. Many agents, chemical or biological, have been identified as sensitising agents (allergens) or irritants. An overview of the chemical and biological agents is given in table 1.

Acute respiratory incidents

Acute respiratory tract injury can be caused by the inhalation of certain agents. Metal fume fever and organic dust toxic syndrome may be caused by high levels of exposure to metal fumes or organic dust, which is contaminated with microorganisms and endotoxins. Both metal fume fever and organic dust syndrome are clinical expressions of intense pulmonary inflammation, which, although relatively benign and transient, should be avoided. These

TABLE 1. Chemical and biological agents associated with different respiratory health effects

Health effect	Agent(s)	Example of job titles involved
Acute respiratory incidents	Toxic gases, vapours or complex mixtures of compounds released from explosions, fires, leaks or spills from industrial installations, transport accidents and military or terrorist operations	Chemical industry workers
	Inhalation fevers (zinc fumes and endotoxins)	Metal workers, agricultural workers
Occupational infections	Tuberculosis pneumonia, zoonoses caused by *Chlamydia psittaci* (ornithosis) *Coxiella burnetii* (Q-fever) and anthrax associated with bio-terrorism	Healthcare workers, butchers, slaughterhouse workers, farmers and post office workers
Asthma	Allergic asthma related to exposure to sensitising agents (di-isocyanates, enzymes, animal, allergens such as cats, dogs and rodents, plant material (*e.g.* wheat flour and latex), metallic agents (*e.g.* platinum salts and cobalt), pharmaceutical agents and reactive dyes)	Car spray painters, farmers, laboratory animal workers, healthcare workers, metal workers, metal refinery workers and workers in chemical industries
	Asthma triggered by inhaled irritants with no specific sensitisation, either following one acute inhalation accident (*e.g.* reactive airways dysfunction syndrome), or due to repeated/chronic exposure to excessive levels of irritants	Healthcare workers, cleaners and firemen
	Asthma-like disorders with no evidence of sensitisation in workers exposed to endotoxin-contaminated vegetable dusts, such as ''brown lung disease'' (byssinosis) in cotton workers or asthma-like symptoms in swine confinement facility workers. This is now more commonly referred to as non-allergic asthma	Agricultural workers
	Work-exacerbated asthma	All professions with any exposure to dust, gases or fumes
COPD	Mineral and organic dusts, and exposure to irritant gases	
Pneumoconiosis	Asbestos, coal dust and silica dust	Miners, construction workers and masons
Respiratory cancers	Asbestos, silica and chromium	Miners, construction workers and welders

reactions are most commonly seen in agricultural work. Surveys of farmers in Sweden and Finland reported that approximately one in 10 farmers has experienced an attack of acute febrile respiratory illness due to exposure to organic dust. The possible long-term effects on those affected are as yet poorly described.

Inhalation of toxic gases, vapours or complex mixtures of compounds that are released from explosions, fires, leaks or spills from industrial installations, transport accidents and military or terrorist operations may lead to more severe tracheobronchial tree and pulmonary

parenchymal injury. Acute inhalation accidents may also occur at home during domestic work, *e.g.* when mixing bleach with acids or ammonia, or when using leather impregnation sprays [9]. Respiratory complications are a major cause of mortality in patients admitted to hospital with burns, which affect from 0.2 to 2.9 inhabitants per million yearly in Europe [10]. Inhalation incidents may take enormous dimensions and affect entire communities.

Toxic tracheobronchitis or pneumonitis with pulmonary oedema can be fatal. These conditions often lead to long-term structural or functional sequelae, such as irritant-induced asthma (reactive airways dysfunction syndrome), in survivors. Those who are at particularly high risk include firemen, emergency personnel and people who work in confined areas.

Exact figures showing the incidence of acute inhalational injuries in the workplace are unavailable. An annual incidence rate of 5 per million for males and 1 per million for females was reported by SWORD [11].

Compared to other workplace injuries, serious inhalation incidents are infrequent; however, appropriate administrative and technical measures are needed in order to prevent them occurring. Disaster plans and adequate facilities must be available at a local level for the management of individual and collective inhalation injuries.

Respiratory infections

Although most respiratory infections are community acquired, they can be directly related to specific occupations. People working in crowded environments, schools, hospitals and other groups may be affected by common viral or bacterial infections. In healthcare workers, TB is a well-recognised risk; however, prison guards or social workers involved with immigrants or asylum seekers originating from areas with TB endemics may also be at risk.

People working in agriculture or other jobs involving direct or indirect contact with animals may be affected by zoonoses, *i.e.* infectious diseases transmitted from animals [12]. Examples of such diseases include ornithosis and Q fever, which are caused by *Chlamydia psittaci* and *Coxiella burnetii*, respectively.

Legionella pneumoniae outbreaks often occur in cooling towers, fountains and whirlpools, or cruise ships, meaning maintenance workers and other personnel are at risk of contracting infection. The spread of anthrax and microorganisms by terrorists is a definite threat in several occupations, *e.g.* postal workers, maintenance workers, law enforcement personnel and healthcare workers.

As demonstrated by the SARS outbreak, emerging infections pose a particular threat to healthcare workers and their families. Over the past few years, the emergence of resistant micoorganisms has become a new problem. In the past, this was only considered to only be a risk for healthcare workers; however, the population risk has broadened to also include agricultural workers and the general public, due to the high use of antimicrobials in livestock production [13].

Although fungi (*e.g. Stachybotrys*) and their mycotoxins may be involved in illnesses caused by flooding or water damage, the role of fungal contamination in water-related occupational respiratory diseases has not been clearly established what [14]. The risk of immunocompromised patients (due to steroid treatment, organ transplantation or other causes) acquiring

invasive fungal infections by ubiquitous fungi, such as *Aspergillus*, is a real problem, but the quantitative relationship between exposure load (in some workplaces) and the risk of becoming infected is still unknown. There is a need to study this relationship and to develop health-based standards of fungal and microbial exposures for the indoor and outdoor environment.

It is also not yet established to what extent microorganisms and biological contaminants, together with indoor climate factors and volatile organic compounds, as well as psychosocial factors, are responsible for outbreaks of sick building syndrome [15]. Sick building syndrome is the occurrence of nonspecific work-related respiratory and other complaints within a large proportion of a workforce working in a sealed, air-conditioned building.

Interstitial lung disease

ILDs have been more closely associated with occupation than any other category of respiratory disease. The classic examples of occupational diseases consist of the pneumoconioses caused by crystalline silica (silicosis), asbestos (asbestosis) and coal dust (coal workers' pneumoconiosis). Less common pneumoconioses do exist and are caused by non-fibrous silicates (talc, kaolin or mica) or other minerals. Pneumoconioses are generally considered to be caused by the progressive accumulation of toxic dust in the lungs. Individual susceptibility and/or immunological sensitisation play a dominant role in the pathogenesis of ILDs, such as extrinsic allergic alveolitis, chronic beryllium disease (berylliosis) or hard metal/cobalt-related lung disease [16].

Silicosis

Occupational aetiology should always be considered in the differential diagnosis of ILDs, particularly in the case of sarcoidosis and idiopathic pulmonary fibrosis, because "occult" exogenous causes are easily missed [17]. Although silicosis should be considered a disease of the past, hazardous exposure to free crystalline silica (quartz or cristobalite) may still occur in mining, tunnel drilling or stone quarrying, stone or sand processing, building and demolition, foundries, pottery or ceramic manufacture, the abrasive use of sand (sandblasting), manipulation of diatomaceous earth, *etc.* [18]. A tragic example of this was reported in Turkey, where hundreds of young workers contracted silicosis as a result of sandblasting denim jeans [19]. The construction industry requires specific attention because there are indications that silicosis has re-emerged in this industry since the introduction of mechanical hand tools, which result in high dust and silica exposure [20]. It is important to realise that silicosis is also associated with other conditions such as COPD, TB, bronchopulmonary cancer and systemic sclerosis. A total of 7200 pneumoconiosis cases were estimated in 2000 in Europe, which were linked to work-related exposure to asbestos, silica and coal dust [1].

In many European countries, thousands of coal miners have developed varying degrees of coal workers' pneumoconiosis. However, the incidence of this disease has declined in past decades and complicated coal workers' pneumoconiosis (or progressive massive fibrosis) should soon become a rarity, at least in western European countries.

Asbestosis

Asbestosis (*i.e.* parenchymal fibrosis caused by asbestos) is now a relatively rare condition. Previously, it was seen amongst people who had been heavily exposed to asbestos in the

workplace in the past, *e.g.* in the manufacture of asbestos-cement products, friction materials or fireproof textiles, or when asbestos was used for heat insulation or fire protection purposes in construction, heating systems, power stations, furnaces, shipyards and railroads. In countries where the use of asbestos in banned, the incidence of asbestosis will, in turn, continue to decrease. However, the risk will remain in developing countries where asbestos use is still permitted and poorly regulated. Those involved in asbestos removal and waste handling will also continue to be at risk. Rigorous enforcement of dust control measures and adequate medical surveillance are key factors in the reduction of the occurrence of this disease.

Sarcoidosis

Sarcoidosis is clinically and pathologically similar to lung disease caused by sensitisation to beryllium (*i.e.* chronic beryllium disease or berylliosis). Although exposure to beryllium exposure is uncommon, it is increasingly being used in modern technology. In a 2006 study of 84 patients with suspected sarcoidosis from Germany and Israel, chronic beryllium disease was diagnosed in 34 subjects [21].

In susceptible individuals, a reaction to cobalt (a constituent of hard metal) causes hard metal lung disease. The disease is characterised by giant cell interstitial pneumonia. Following the introduction of polishing disks made of diamond-cobalt, the disease was reported among diamond polishers in Belgium. Although hard metal lung disease is not commonly reported, cases have been described in small workshops where hard metal or diamond-cobalt tools are manufactured or sharpened [22].

Several other metals have been associated with ILD and are occasionally misdiagnosed as sarcoidosis; however, the epidemiology of these rare conditions is poorly described. More effort is needed at a European level to recognise, register and prevent these conditions.

Extrinsic allergic alveolitis

The occupational causes of extrinsic allergic alveolitis (or hypersensitivity pneumonitis) are diverse, with the more frequent aetiologies including organic dusts originating from microorganisms (farmer's lung and humidifier's lung) or birds (pigeon breeder's lung and bird fancier's lung). However, in all environments in which inhalation of bio-aerosols is possible, this should be considered as a potential cause of extrinsic allergic alveolitis. These environments include mushroom farms, composting installations, wood processing plants, vegetable storage, machine workshops (through the use of machining fluids), *etc.* Some chemicals, most notably isocyanates, may also cause the condition.

Occupational extrinsic allergic alveolitis is most commonly studied in farmers, in whom the disease is caused by sensitisation to (thermophilic) microorganisms that grow in hay or other organic substrates. There is a considerable geographic variation in the frequency of farmer's lung, which is dependent on climatic factors and farming practices. The causative antigens also differ between regions. Farmer's lung occurs most frequently in cold, humid climates of northern Europe or in mountainous areas like the Doubs (France). Depending on area and diagnostic criteria, the reported prevalence rates vary between 10 and 200 per 100 000 inhabitants and 4–170 per 1000 farmers. In the 1980s, yearly incidences were estimated to be 2–6 per 1000 farmers and 5 per 1000 farmers in Sweden and Finland, respectively [23]. However, this may be an underestimation due to diagnostic problems and the use of hospital

data. Extrinsic allergic alveolitis outbreaks have also been described among workers exposed to metal working (or machining) fluids, *e.g.* in the manufacture of car engines [24, 25]. The exact aetiological agent cannot always be identified but bacteria including mycobacteria have been implicated.

Asthma and work-exacerbated asthma

Occupational asthma is a disease characterised by airway inflammation and variable airflow obstruction caused by a particular work environment, not stimuli encountered outside the workplace. This condition can be associated with BHR but this is not always the case. Work-exacerbated asthma is pre-existing asthma that is worsened by exposures in the occupational environment, which are not causally related to the occurrence of asthma in the individual but are capable of worsening symptoms. To the individual there is no difference in the symptomatology. Work-exacerbated asthma probably causes the greatest health burden, due to the increasing proportion of the European population that suffer from asthma when entering the job market.

Only a few population-based prospective studies of occupational asthma exist. The most recent of these is based on the European Community Respiratory Health Survey (ECRHS) cohort, which followed 7000 people for 10 years [26]. This study found an incidence of 250–300 new cases per 10 million person years, which should be compared to the 200 occupational asthma cases per million person years in Finland, which probably has the most comprehensive surveillance scheme for the detection of occupational asthma worldwide.

Occupational asthma can be caused by low- and high-molecular weight compounds, and more than 200 such sensitisers have been identified as causing occupational asthma [27, 28]. High-molecular weight sensitisers most often give rise to immunological occupational asthma *via* the induction of IgE antibodies to one or more epitope on the surface of the allergen. This is illustrated by employees in the pharmaceutical industry, where the majority of workers contract sensitisation and allergic symptoms at very high rates in the early days of production [29]. Occupational asthma caused by low-molecular weight sensitisers is exemplified by the induction of asthma symptoms in spray painters exposed to isocyanate in paint and welders or soldering workers who develop asthmatic symptoms due to welding fumes or colofonium smoke [30].

Work-exacerbated asthma is a common and under-recognised adverse outcome resulting from conditions at work. According to the National Institute for Occupational Safety and Health in the USA, work-exacerbated asthma is common, with a median prevalence of 21.5% among adults with asthma. Hence, it is an even a bigger problem than occupational asthma for workers in industries in which they are exposed to airway irritants [31].

Prognosis

A recent publication, using data from the ECRHS study, showed that occupational exposure to asthma-causing agents is associated with uncontrolled adult-onset asthma [32]. Likewise, another study showed that adult-onset asthmatics had an increased risk of disability (prevalence ratio 2.40 (95% CI 1.70–3.40)) [33]. It is still debated whether reducing exposure is acceptable as an intervention strategy compared with removal from exposure [34]. A complication in the interpretation of the available evidence is that few studies characterised exposure objectively and quantitatively.

COPD

The predominant cause of COPD is cigarette smoking; however, occupational exposures to mineral dusts, organic dusts, irritant gases and vapours contribute to the incidence and the severity of chronic airway diseases, including COPD. There was an intense debate in the late 1970s and 1980s about the role of occupational exposures in the development of COPD [35–42]. It was debated whether occupational exposures (for example, mineral dust exposure in (coal) mining) could lead to clinically relevant reductions in lung function in nonsmokers. As a response to this discussion, general population studies began to explore the association between occupational exposures (characterised by the level of job titles or by the first applications of the so-called "job exposure matrix") and COPD, which was measured by respiratory symptoms and lung function.

The most common respiratory manifestation of exposure to dusts or fumes consists of the presence of chronic bronchitis, *i.e.* "industrial bronchitis". As is the case with cigarette smoking, industrial bronchitis may or may not be associated with airflow limitation, as assessed by a decrease in FEV_1. Several longitudinal studies have shown that exposure to coal mine dust is associated with a loss of ventilatory function, even in the absence of pneumoconiosis [43]. Although the average loss of function appears to be small, it can be comparable to the changes in lung function attributable to smoking that were found in population studies; these loses occur across the whole population [44]. Some individuals even suffer substantial and clinically significant impairment. In addition to underground mining, other occupations with exposure to mineral dusts (such as builders) or fumes (such as welders) may also be at risk of occupationally induced COPD; however, the epidemiological evidence is generally not as strong for these categories of workers. It is often under-appreciated that exposure to agricultural dusts (such as grain dust, vegetable fibres or animal feed) is also a significant cause of chronic airway disease [45]. The prevalence of chronic bronchitis in farmers, particularly swine confinement farmers and dairy farmers, is particularly high, even among nonsmoking farmers. Accelerated decline in lung function has been observed in these populations with ongoing exposure [46].

In general, population-based studies have supported the findings from workplace-based studies, particularly with regard to dusty jobs or jobs involving mixed exposures to dusts and gases. However, the quantitative contribution of occupational factors to the burden of COPD morbidity or mortality has not been evaluated as extensively. In Finland, an attributable fraction of 11.7% (14.0% in males and 3.8% in females) has been estimated for work-related COPD mortality [3].

Respiratory cancers

Malignant mesothelioma is a pleural (or less frequently a pericardial or peritoneal) tumour that, in most cases, is caused by occupational or environmental asbestos exposure. The latency between exposure and the clinical manifestations of mesothelioma is usually 30 years or more, and the tumour may even occur after brief or low exposures. It has been predicted that the increase in the occurrence of malignant mesothelioma, which has paralleled the industrial use of asbestos, will continue until approximately 2020 in most European countries, killing about a quarter of a million people between 1995 and 2029 [47]. According to this prediction, one in 150 males born between 1945 and 1950 will die of this "rare" tumour, for which no effective cure is presently available.

More than 90% of mesothelioma cases are related to asbestos and occupational exposure is the major contributor to its occurrence. A recent UK case–control study provided a detailed overview of occupations that are at high and low risk for developing mesothelioma, many of which are in the construction industry and other traditional professions in the production industry and ship building [48]. There is considerable variation in mesothelioma mortality rates between countries, and these rates have been shown to correlate strongly with the amount of asbestos imported into a country [49]. Mortality rates vary more than 10-fold between European countries. This variation most likely reflects the differences in asbestos use post-World War II, although for low rates in some countries might also be associated with diagnostic issues (fig. 1). In some countries, environmental sources have been identified resulting in disease associated with environmental asbestos exposure.

The role of occupational exposure as a cause of lung cancer (other than mesothelioma) has been investigated by several epidemiological studies. Despite the difficulties of such studies, several occupational agents (or jobs) have been identified as definite or probable causes. The well-established lung carcinogens (belonging to category 1 of the World Health Organization, International Agency for Research of Cancer classification) include: asbestos fibres; some chromium(VI) compounds; some nickel compounds; arsenic; radon gas and its decay products (radon daughters); bis(chloromethyl)ether; and crystalline silica (occupational exposure). Depending on the agent and the methodological aspects, additive or multiplicative modes of interaction have been shown to occur with concurring cigarette smoking. Coke production and coal gasification (possibly related to polycyclic aromatic hydrocarbons), iron and steel founding, paint manufacture and painting are established carcinogenic processes that are related to lung disease. Work-related exposure to diesel exhaust and environmental tobacco smoke are also causes of lung cancer, although the magnitude of the risk is smaller than that found for other established carcinogenic agents. The population at risk within the workforce for exposure to agents such as diesel is large, thus leading to a potentially substantial burden of disease [50].

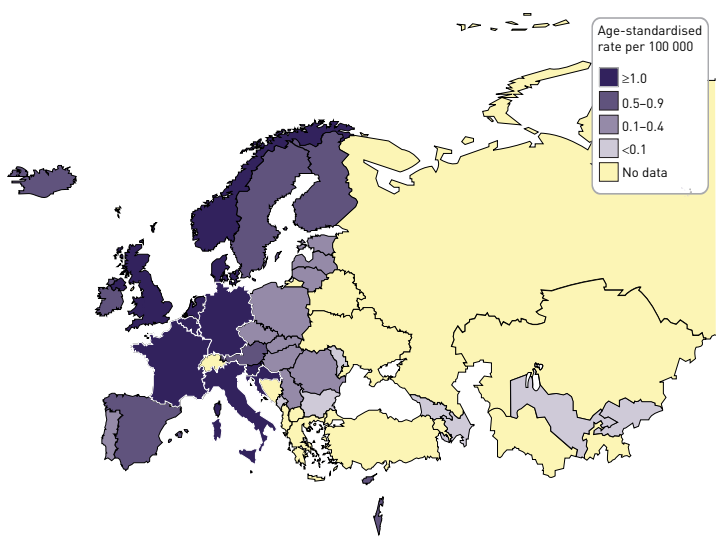

Figure 1. Age-standardised mortality rates for mesothelioma per 100 000 population. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update. Reproduced from [8] with permission from the publisher.

Compared with other common cancers, the role of occupational exposure as a cause of lung cancer has been shown to be considerably large. Estimates are frequently reported to be 15% and 5% for males and females, respectively [51]. In Finland, higher population attributable risks have been reported for occupational exposure's role in bronchopulmonary cancer (24% overall, and 29% and 5% in males and females, respectively) [3]. Occupational asbestos exposure is considered the most influential factor in all studies. A prospective cohort study from the Netherlands estimated that, in males, 12% of lung cancer cases were attributable to a lifetime of occupational asbestos exposure, after adjustment for smoking and diet [52]. In Europe, the total burden of lung cancer cases attributable to work-related exposure to respiratory carcinogens is estimated to be 32 400 cases per year [53].

Despite the high estimates of the contribution of occupational factors to the aetiology of lung cancer, compensation agencies or notification systems have stated that very few cases of lung cancers of occupational origin are reported. Such under-reporting is due to the following: 1) occupational lung cancer often occurs among (former) smokers; 2) clinical presentation of occupational lung cancer is generally similar to nonoccupational lung cancer; 3) therapeutic options do not differ between occupationally induced and nonoccupational lung cancer; and 4) causal conclusions in an individual patient have to be based on estimated probabilities that the disease is work-related. However, in terms of prevention, the notion of occupationally induced lung cancer is important, and efforts need to continue in Europe in order to detect and reduce occupational carcinogenic exposures.

New risks

There is a long history of new products/production methods being connected with occupational lung diseases, with new diseases occurring soon after their introduction. Examples of this include the re-occurrence of early signs of silicosis in construction workers [20], acute lethal silicosis in unprotected textile workers involved in the production of sandblasting jeans [19], new synthetic fibres like nylon microfibres that cause nylon flock fibrosis [54–56], and organising pneumonia called "adystil syndrome", which is caused by aerosolised paints in printing shops in the textile industry [57, 58]. An equally severe outbreak has been associated with artificial butter flavouring. This was first observed in popcorn workers, hence the name "popcorn worker's lung" [59]. However, this has now been reported in workers producing the artificial butter flavour [60]. Furthermore, a patient from Colorado, USA, who had been preparing several packets of microwave popcorn a day for a number of years, fell ill with the same disease.

Economic burden

The population attributable risk for work-related asthma and COPD is approximately 15%. Since these diseases are common, the economic burden related to a population attributable risk of this size amounts to a substantial burden on public health. In 1998, the European Agency for Safety and Health at Work published a report on the economic impact of occupational health in the EU member states [61]. The study explored methodologies in different countries but did not give specific estimates. An economic analysis based on population attributable risks from a US study showed that the cost of occupationally caused asthma and COPD would be approximately €5 billion annually, not taking into account pneumoconioses and malignant lung diseases [62]. Translation of these figures to the European area would amount to an annual cost of approximately €6.4 billion in the 28

contemporary member states of the EU, including the new member states. These figures do not take into account the loss of productivity and health related to increased morbidity in the rising proportion of the European population with pre-existing asthma and allergies.

According to a study of the economic burden of cancer in the EU, lung cancer had the highest economic cost, at €18.8 billion annually. Due to the relatively young age of onset, lung cancer also contributed to the highest productivity losses attributable to mortality of €9.92 billion, which is comparable to 23% of the total €42.6 billion in productivity losses due to all cancers [53]. The Global Burden of Disease project calculated the attributable fraction for lung cancer caused by workplace exposure in the EU to be 6% (7% and 2% for males and females, respectively).

If the cost of lung cancer caused by occupational exposure was calculated as the attributable fraction multiplied by the total cost for lung cancer, the economic burden of occupational lung cancer would be in the region of €1.13 billion annually. However, this estimate does not take into account the more than 1100 cases of mesothelioma annually, as projected by the Global Burden of Disease project [1, 53]. This estimate is in itself a highly conservative estimate for the number of mesothelioma cases in western Europe and actually underestimates the number of cases when compared with the number of cases reported in some of the larger western European countries. Thus, the costs related to malignant respiratory cancer are expected to be grossly underestimated.

In total, the economic burden of occupation-related respiratory diseases is exceeding €7.5 billion annually. Even if the calculations are somewhat uncertain, the figures reflect a disease that is preventable and, therefore, this economic burden should be kept to a minimum.

Regulatory aspects and prevention

In principle, occupational diseases are more amenable to prevention than diseases caused by genetic or lifestyle factors, or the general environment. Legal and technical frameworks exist in the EU and its member states that are specific to the work environment. Occupational exposure standards exist for major hazards, and these define the level of pollutant under which no major health risks are expected. These standards are proposed by the Scientific Committee on Occupational Exposure Limits at the European level. So-called "derived maximum exposure levels" are usually obtained for carcinogens; these describe the level below which the likelihood is reduced. A lifetime excess risk of 1 per 250 is an acceptable risk and 1 per 25 000 is a negligible risk. Unfortunately, the standard setting process at the EU level is slow and not all standards are up to date. Most attention has been given to mineral dusts and carcinogens, and it was felt that it was not possible to set a safe level for allergens. However, it has been recognised that a minimal effect or risk approach is feasible and the opinion on risk assessment for allergens is changing [63, 64]. There is now a growing consensus that exposure standards for allergens are achievable. Individual member states are also active in standard-setting processes but there is a need for European standardisation and especially coordination.

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Chapter 17

Diet

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Several lung diseases may be related to dietary intake changes. Dietetic hypotheses have primarily related antioxidants, vitamin D, polyunsaturated fatty acids and dietary patterns (mainly the Mediterranean diet) with the pathophysiological events related to various lung diseases. Asthma has been related to reduced antioxidant intake and decreased omega-3 to omega-6 ratio; however, the beneficial effect of nutrient supplementation in asthma remains to be proven. Vitamin C may be related to better lung function, while β-carotene intake has been associated with increased lung cancer incidence in smokers and should be used with caution. Active TB risk is increased in subjects with vitamin D deficiency, but the role of vitamin D manipulation in TB prevention and treatment remains to be established. A Mediterranean diet is unequivocally associated with reduced lung cancer incidence. Further high quality investigations are needed in order to substantiate the nature and the importance of various nutrients as risk factors for lung health and disease.

Nutrition, an important aspect of everyday life, may affect lung development. Several studies have suggested that dietary factors may be implicated in the pathophysiological events that lead to the pulmonary dysfunction responsible for lung diseases. Although dietary modification is further complicated by changes in body weight, this chapter will focus on the effects of the most important dietary nutrients or nutrient groups in the most common respiratory diseases.

Diet and lung disease

Antioxidants

Oxidative stress underlies a number of obstructive, inflammatory and fibrotic lung diseases [1]. Thus, nutrients with antioxidant capacity may enhance natural defences and protect against oxidative stress associated with various lung diseases, cigarette smoking or air pollution. Non-enzymatic antioxidants are found in foods. Vitamin C (ascorbic acid) is an essential water-soluble vitamin derived from the diet that acts as an oxygen radical scavenger and, due to its antioxidant capacity, it stabilises a number of compounds including vitamin E and folic acid (table 1) [2]. In addition, vitamin C enhances the function of phagocytes and the proliferative capacity of T-lymphocytes. Food sources of vitamin C include citrus fruits, strawberries and spinach [3]. Vitamin E (α-tocopherol) is a fat-soluble compound acting as a free radical scavenger that protects polyunsaturated fatty acids (PUFAs) from peroxidation.

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Table 1. Dietary sources of the main nutrients

Nutrient	Source	Comments
Vitamin C	Citrus fruits, strawberries, tomatoes, potatoes, Brussels sprouts, broccoli, spinach	• Water-soluble vitamin • Derived only from diet • Oxygen radical scavenger • Immunomodulatory effects
Vitamin E	Vegetable oils, eggs, leafy vegetables	• Fat-soluble vitamin • Oxygen radical scavenger
Vitamin A	Liver, kidney, egg yolk, butter	• Preformed vitamin A
β-carotene	Leafy vegetables, carrots, sweet potatoes	• Provitamin A • Oxygen radical scavenger • β-carotene supplementation is associated with increased lung cancer risk in smokers
Vitamin D	Oily fish, cod liver oil, fortified grains, dairy products	• Main source is sun exposure, minimal contribution from dietary intake • Immunomodulatory effects • Microbial killing properties • Reduced levels are associated with increased active TB risk
Omega-3 PUFAs	Oily fish, cod liver oil	• Decreased synthesis of prostaglandin E2 and leukotriene B4 • Omega-3 to omega-6 ratio more important

PUFA: polyunsaturated fatty acid.

Studies concerning its role in the immune system are inconsistent [4]. Vitamin E is found in vegetable oils, eggs and leafy vegetables. Vitamin A (retinol) belongs to a subclass of fat-soluble compounds known as retinoic acids [5]. β-carotene is a form of provitamin A found in leafy vegetables, carrots and sweet potatoes. Retinol (preformed vitamin A) is found in liver and eggs. Selenium is an essential trace element important in various biological functions including antioxidant defence, and is found in seafood, liver and seeds in amounts that vary according to the levels of selenium present in water [6].

Asthma

Asthma prevalence has increased in most industrialised countries and reached a plateau in 2000, possibly due to changes in lifestyle and environment. An emerging hypothesis has proposed that a decline in dietary antioxidant intake may have contributed to the increase in asthma [7].

Observational studies have suggested an association of antioxidant deficiencies with asthma risk. Asthma has been related to low vitamin E intake [8], and asthma patients present with reduced selenium and carotenoid concentrations [9, 10]. Low vitamin A and vitamin E intake has been associated with severe asthma [11] and vitamin C consumption has been inversely associated with asthma risk [12]. Two recent meta-analyses of epidemiological studies have reported conflicting data: the first reported no significant association between antioxidants

and asthma [13], and the second suggested that low dietary intake of vitamin A and C is related to asthma and wheeze, with the differences among the studies possibly due to methodological discrepancies [11].

Interventional studies have shed light on the role of antioxidants in asthma. Recently published meta-analyses suggest that the evidence from randomised controlled trials (RCTs) is insufficient to provide a strong recommendation of vitamin C supplementation for asthma [14] or exercise-induced bronchoconstriction [15]. Similarly, selenium supplementation does not confer a clinical benefit in asthmatics [16], while vitamin E has no beneficial effect on BHR [17]. A recent open-label study on multiple nutrient supplement therapy in allergic asthma, including various antioxidants, showed improvements in pulmonary function and health-related quality of life [18].

Overall, the available data regarding the role of antioxidants in asthma are inconclusive. The beneficial effect of dietary antioxidant supplementation on current asthma treatment has not been proven, although studies have shown individual effects on oxidant status and immunoregulation [19].

Chronic obstructive pulmonary disease

The systemic inflammation associated with COPD may be partially triggered by the aggravated oxidative stress that is prevalent in the disease. Thus, balancing oxidative stress through diet may protect against the development of COPD [20]. Epidemiological studies have almost unequivocally suggested that vitamin C intake is beneficially associated with lung function, irrespective of smoking intensity [21]. Similarly, vitamin E intake showed a significant positive association with FEV_1 and FVC with a dose-dependent response [22]. However, others have challenged the relationship between vitamin E and lung function [23]. β-carotene is positively associated with FEV_1 [23] and was associated with a slower decline of FEV_1 in an 8-year follow-up [24].

Few interventional studies have evaluated the impact of antioxidants. Supplementation with α-tocopherol and β-carotene confers no benefit in terms of COPD symptoms and chronic bronchitis diagnosis [25]. A *post hoc* analysis of vitamin E supplementation in almost 39 000 females did not demonstrate a reduction in the diagnosis of chronic lung diseases, including COPD [26]. In another *post hoc* analysis of vitamin E supplementation in patients with coronary disease, there were no effects on pulmonary function or COPD/asthma hospitalisation rates [27]. Taken together, the data suggest that antioxidants, and especially vitamin C, may be related to better lung function; however, the role of antioxidant nutrients in COPD has yet to be explored. Exploration of their role should be carried out with caution due to the safety concerns associated with increased lung cancer prevalence [28].

Lung cancer

Observational data have suggested that antioxidant nutrients may be implicated in the development of lung cancer. Intake of vitamins A, C and E has a protective effect on lung cancer development, with modification of the effect by smoking habit [29]. In agreement with this data, carotenoids and vitamin E, but not vitamin C, have been shown to reduce the risk of lung cancer [30]. However, these findings have not been replicated in human interventional settings. In a double-blind RCT, involving almost 30 000 smoking males followed up for 5–8 years, β-carotene supplementation was associated with higher incidence of lung cancer and increased mortality, especially in heavy smokers and alcohol abusers, while males receiving vitamin E showed no reduction in lung cancer incidence [31]. Other

studies have shown that vitamin C supplementation does not confer any benefit in terms of lung cancer prevention, while vitamin E supplementation may be harmful [32]. In addition, a systematic review suggested that selenium supplementation may be beneficial for subjects with low selenium levels [33]. Selenium may also reduce the toxicity associated with cisplatin [34]. Overall, the available data do not provide evidence of any measurable preventive effect in lung cancer.

Respiratory infections

Several antioxidants have immunomodulatory roles; therefore, they may be implicated in the development and outcome of respiratory infections [35]. Deficiencies in micronutrients, including vitamin C, vitamin E and zinc, may be associated with a higher burden of respiratory infections, possibly due to an impaired immune response [36]. In two relatively recent Cochrane meta-analyses, vitamin A did not confer a significant benefit in preventing LRTIs [37], while vitamin A supplementation did not significantly reduce morbidity or mortality or affect the clinical course of pneumonia in children [38]. Vitamin C, vitamin E, β-carotene and zinc are not related to common cold incidence [39, 40]. Vitamin E and β-carotene supplementation do not influence the risk of severe hospital-treated pneumonia [41], although some have reported that vitamin E might increase the risk of pneumonia in patients with increased vitamin C intake [42]. In a RCT in 2004, vitamin E supplementation did not significantly affect LRTIs [43]. The results remain imprecise and warrant further investigation before definite conclusions are drawn.

Vitamin D

Vitamin D has attracted a lot of attention due to its significant immunomodulatory effects. Most of the dietary vitamin D is found in oily fish, cod liver oil and dairy products [44], although it is mainly derived from sun exposure.

Besides its well established role in bone and calcium homeostasis, vitamin D has the ability to suppress T-helper cell (Th) type 1 and enhance Th2 immune responses [44] and promote IL-10-secreting regulatory T-cells [45]. In addition, vitamin D induces the production of antimicrobial peptides such as cathelicidin [46] and, thus, may reduce infection severity or prevalence. Vitamin D is also involved in tissue remodelling [47].

Asthma

Epidemiological studies have demonstrated that vitamin D deficiency is common among asthmatics [48]. In addition, serum vitamin D has been negatively correlated with airway responsiveness to methacholine and exercise-induced bronchoconstriction [49], while low vitamin D has been associated with airway remodelling as reflected by increased airway smooth muscle mass [50]. In one respect, vitamin D may be implicated in the manifestations of the disease in already established asthma. A large number of studies have demonstrated that low vitamin D levels are more pronounced in severe asthma [51]. In addition, vitamin D levels are positively associated with lung function and negatively associated with asthma control as indicated by exacerbation rate and asthma hospitalisations [50, 52–54]. There is evidence that vitamin D enhances responsiveness to steroids. In steroid-resistant asthmatics, supplementation with vitamin D enhances the ability of regulatory T-cells to secrete IL-10 in response to steroids [45]. Clinical trials have confirmed this finding by demonstrating that reduced vitamin D levels are associated with a reduced steroid response [48, 55]. To summarise, the current data provide supporting evidence for a beneficial role of vitamin D in

asthma but cannot establish causality, due to the cross-sectional nature of the studies. To our knowledge there are no RCTs in this field.

Chronic obstructive pulmonary disease

The role of vitamin D in COPD has not been fully explored. Studies have demonstrated deficient levels of vitamin D in COPD subjects [56, 57], which may correlate with disease staging and severity [56] but not with mortality [57]. Interestingly, vitamin D deficiency accelerated emphysema in cigarette smoke-exposed mice, possibly through an increased protease/antiprotease ratio [58]. The mechanisms linking vitamin D deficiency to COPD are not clear and need to be investigated. The association may implicate the calcaemic effects of vitamin D (*i.e.* osteoporosis causing thoracic vertebral fractures and, thus, limitations in pulmonary function), alterations of the immune response and tissue remodelling [59].

In one respect, the ability of vitamin D to downregulate the immune response in the airways and upregulate the innate immune defence against microbes may contribute to the occurrence of COPD exacerbations [59]. However, this hypothesis has not been confirmed. In a prospective study, vitamin D levels did not influence exacerbation rate or the time to first exacerbation during a 1-year follow-up [60] and were not associated with frequent exacerbations [61]. Vitamin D supplementation had no effect on exacerbation frequency or time to first exacerbation except in a subgroup of patients with severe vitamin D deficiency who showed a significant reduction in exacerbations [62].

Lung cancer

Vitamin D may exhibit anti-carcinogenic effects *via* the inhibition of cell proliferation and angiogenesis, and the enhancement of apoptosis and cell differentiation [63]. However, studies have failed to demonstrate an inverse association between vitamin D levels and lung cancer risk [64], although some have shown a beneficial effect in females only [65] and in never-smokers [66]. Low serum 25-hydroxyvitamin D (25(OH)D) levels are associated with worse mortality in lung cancer [67], although other studies have reported a significant inverse association with mortality only in a subgroup of nonsmokers [68]. However, results from the National Health and Nutrition Examination Survey (NHANES) III study in the USA have suggested a positive association between vitamin D and lung cancer mortality in males [69].

Data from animal and *in vitro* studies have suggested that vitamin D may have a protective effect against lung cancer growth and metastatic ability *via* the secretion of E-cadherin and catenin, which increase the adherence of malignant cells and reduce the probability of mobilisation of cancer cells to other sites [70]. The literature lacks data from well-designed studies and the causal direction of the these results cannot be established.

Tuberculosis

Several studies have addressed the association of vitamin D deficiency and TB. Observational studies have shown a positive association between low levels of vitamin D and TB prevalence [71], while serum vitamin D concentrations are inversely correlated with time to sputum smear conversion and are decreased in multidrug-resistant TB [72]. Adequate vitamin D levels are associated with decreased relapses [73]. In a 2008 meta-analysis of observational studies, low vitamin D was found to increase the risk of active TB [74], possibly through cathelicidin-mediated mycobacterial killing [75].

In a placebo-controlled RCT, adjuvant vitamin D supplementation resulted in an accelerated reduction of radiographic findings and greater weight gain [76], a higher rate of sputum

conversion to culture negativity [77], and improved cell-mediated immunity against *Mycobacterium tuberculosis* [76]. Other studies have reported no differences in clinical, radiological or laboratory parameters, possibly due to inadequate sample size and low dosages [78, 79]. To date, the evidence suggests that low vitamin D levels are associated with increased active TB risk; however, the data regarding vitamin D supplementation in combination with anti-tuberculous drugs are controversial.

Respiratory infections

Insufficient levels of vitamin D have been associated with an impaired risk of respiratory infections. In a secondary analysis of the NHANES III, consisting of 18 883 subjects, 25(OH)D levels were inversely associated with upper respiratory tract infections, with a dose–response association, especially in asthma and COPD patients [80]. Similar results have been obtained in other studies [81, 82]. Children with vitamin D deficiency were more likely to be admitted to the ICU, although vitamin D was not associated with infection occurrence [83]. In a recent systematic review of observational studies, vitamin D levels were predominantly associated with increased risk of upper and lower respiratory infections [84], while vitamin D receptor polymorphisms have been implicated in the risk of developing ALRIs [85].

The data from the RCTs available concerning the effect of vitamin D in infection prevention and outcomes are not clear. Some studies have reported that administration of vitamin D does not significantly reduce the frequency or the severity of acute upper respiratory tract infections [86], and does not affect the duration of the resolution of pneumonia [87]. In contrast, vitamin D supplementation may have a preventive effect against influenza infection [88] or all-cause respiratory infections [89]. At this time, the importance of vitamin D deficiency in respiratory infection appears significant; however, the beneficial effect of vitamin D supplementation is not clear. High quality studies are warranted to establish the role of vitamin D manipulation in respiratory infections.

Polyunsaturated fatty acids

PUFAs are divided into omega-3 (n-3) and omega-6 (n-6) fatty acids and they have important immunomodulatory and inflammatory effects since they are incorporated into membrane phospholipids of immune cells and affect the synthesis of eicosanoids and docosanoids. The omega-3 PUFA α-linolenic acid (ALA) is metabolised endogenously into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while the omega-6 PUFA linoleic acid gives rise to arachidonic acid, a precursor of prostaglandin E2 and leukotriene B4, which have proinflammatory properties [90]. Omega-3 PUFAs antagonise arachidonic acid as potential substrates of cyclooxygenase and lipoxygenase, reducing the production of proinflammatory eicosanoids and, thus, exerting immunosuppressive effects [90]. Omega-3 PUFAs are found in fresh oily fish (*e.g.* tuna and salmon) and cod liver oil, while omega-6 PUFAs are present in large amounts in vegetable oils and margarines. In the western diet, omega-3 consumption has decreased while omega-6 intake has increased, possibly due to public campaigns focused on chronic heart disease control [91].

Asthma

The increased intake of omega-6 PUFAs and decreased intake of omega-3 PUFAs associated with modern diet may contribute to the development of airway inflammation and, consequently, asthma [91]. EPA is a potential cyclooxygenase substrate that antagonises arachidonic acid metabolism and inhibits prostaglandin E2 synthesis [91]. Thus, the

competitive actions of omega-3 and omega-6 in inflammation may alter the balance of eicosanoids produced and the ratio of omega-3 to omega-6 fatty acids may contribute to the development of asthma [92]. High omega-3 to omega-6 ratio has been associated with improved methacholine-induced provocative dose and lower leukotriene urinary excretion [93]. Other studies have failed to exhibit an association of PUFAs with asthma [8].

Intervention studies have revealed inconsistent results. In a small cohort, omega-3 supplementation resulted in reduced exercise-induced bronchoconstriction, possibly through a reduction in inflammatory markers such as prostaglandin D2 and leukotriene B4 [94]. In contrast, SCHUBERT *et al.* [95] did not demonstrate improvements in symptoms or lung function following omega-3 supplementation in house-dust mite-sensitised asthmatics.

Chronic obstructive pulmonary disease

Individual PUFA intake may protect smokers from COPD development, but the data are sparse. High dietary intake of omega-3 is inversely related to COPD risk in a dose-dependent manner [96], but not consistently [97]. In a large-scale cross-sectional investigation, DHA and omega-6 intake was inversely associated with FEV_1 [97]. Interestingly, higher intake of omega-3 has been associated with lower TNF-α levels, and omega-6 consumption has been related to higher IL-6, indicating that PUFA consumption may directly interfere with COPD-related inflammation [98]. Unfortunately, RCTs are lacking. PUFA supplementation exerts beneficial effects on exercise capacity in COPD patients undergoing a rehabilitation programme; however, the effect of PUFAs on COPD prevalence or severity has not been studied [99].

Infections

In a prospective study, high intake of ALA and linoleic acid was associated with a reduced risk of pneumonia [100], while others have failed to replicate such an association [101]. Dietary supplementation with DHA and arachidonic acid results in lower incidence of upper respiratory tract infections, through a reduction in viral infections [102]. In this context, DHA and arachidonic acid supplementation of formulas for infants have been related to a reduced incidence of upper airway infections [103]. By contrast, others have demonstrated that EPA and DHA intake is not associated with pneumonia risk [100]. To summarise, the data available concerning the effect of PUFAs in respiratory infections are inconsistent and await clarification.

As far as *M. tuberculosis* infection is concerned, the impact of PUFAs is not well studied. Omega-3 PUFAs may reduce host resistance to *M. tuberculosis* in experimental settings through impaired interferon-γ-induced activation of macrophages [104]. Omega-3-fed guinea pigs exhibit reduced *in vivo* skin test positivity and less robust inflammatory responses in the lungs following *M. tuberculosis* infection [105]. *In vitro*, macrophages infected with *M. tuberculosis* and incubated in DHA display defective macrophage activation and a reduced ability to control the infection [104], while omega-6 PUFAs stimulate TNF-α secretion by macrophages [106]. Finally, omega-3-enriched transgenic mice exhibit higher bacterial loads and a reduced inflammatory response [107]. The available experimental data support the hypothesis that omega-3 PUFAs may increase susceptibility to TB; however, well-designed clinical studies are lacking.

Lung cancer

Omega-3 fatty acids have been related to lower prevalence of various types of cancer, but the data regarding lung cancer are limited. The possible protective effects have been suggested by

in vitro studies, where omega-3 PUFAs were found to inhibit proliferation and induce the apoptosis of lung cancer cells [108]. Epidemiological studies have suggested that cod liver oil supplementation is associated with lower lung cancer risk after adjustment for smoking status [109]. RCTs have suggested that omega-3 supplementation as adjuvant therapy may beneficially affect nutritional status [110], performance status and physical activity in lung cancer patients [111]. To date, the data are limited and no definite conclusions can be drawn regarding the role of PUFAs in lung cancer.

Healthy diet *versus* nutrients: the role of dietary patterns

Recently, the term "dietary pattern" has emerged in the literature. Traditionally, research has concentrated on single nutrients (table 2); however, this type of analysis has some methodological limitations. Diet is a complex variable and humans consume a variety of foods with complex combinations of nutrients and possible interactive or synergistic actions [112]. Single nutrient effects may be too small but the cumulative effect of various nutrients present in foods may be sufficient to provide a significant effect [112]. To overcome these limitations, "dietary pattern" studies have emerged, addressing how habitual eating behaviours, with their respective food and nutrient combinations, are associated with diseases. A possible drawback of this approach is that it cannot estimate the effects of single nutrients and that it may confound other lifestyle patterns.

Asthma

The majority of observational studies suggest that higher consumption of fruit and vegetables and greater adherence to a Mediterranean diet (low consumption of alcohol, meat and dairy products and high consumption of fruits, vegetables, legumes and PUFAs) during pregnancy or childhood may result in reduced risk of asthma or wheeze [113]. Few clinical trials exist addressing the association of the Mediterranean diet in adult life with asthma. In a small RCT, adherence to the Mediterranean diet showed nonsignificant improvements in lung function and asthma control [114]. In addition, observational studies have indicated that fish consumption protects against asthma symptoms [115] and asthma *per se* [116]. Moreover, high meat or "processed" meat intake during pregnancy may increase the risk of wheeze in children [117].

Chronic obstructive pulmonary disease

Fresh fruit consumption has a positive dose–response relationship with pulmonary function and is associated with reduced prevalence of COPD symptoms [118], while a reduction in fresh fruit intake is associated with a greater decline in FEV_1 [119]. In the MORGEN (monitoring project on risk factors for chronic diseases) study, fruit and wholegrain intake was independently and beneficially associated with COPD outcome, while fish and vegetable intake was not [120]. Other studies have observed that vegetable and fruit intake is inversely associated with COPD [121]. Subjects consuming a "prudent diet" (consisting of high amounts of fruit, vegetables, oily fish and wholemeal cereals) have a lower prevalence of COPD and better lung function [122]. Interestingly, in a randomised intervention study of COPD patients, a dietary shift to foods with higher antioxidant content (fruit and vegetables) over a period of 3 years resulted in an annual increase of FEV_1 [20].

Table 2. The role of various nutrients in lung diseases

Disease	Main findings	Comments
COPD	Vitamin C intake is positively associated with lung function [21]	Cross-sectional studies
	Reduced vitamin D levels associated with increased COPD prevalence [56, 57]	Insufficient data, small number of studies
	Omega-3 intake reduces COPD risk [96]	Cross-sectional studies, no RCT available to test the results
Asthma	Deficient antioxidant levels [8–11]	Cross-sectional studies, RCTs provide inconsistent data
	Vitamin D is reduced in severe asthma and negatively associated with asthma control [50–54]	Cross-sectional studies
	Omega-3/omega-6 ratio is associated with reduced methacholine-induced provocation dose [93]	Intervention studies not consistent
Lung cancer	β-carotene supplementation is associated with increased risk [31]	β-carotene supplementation may be harmful in smokers
	Omega-3 supplementation improves performance status [111]	Limited studies, association with lung cancer risk not well studied
TB	Low vitamin D related to increased risk [74]	Cross-sectional studies, inconsistent results among studies, mechanism of action not fully elucidated
	Vitamin D levels inversely related to outcome [72, 73]	
	Vitamin D supplementation improves outcome [76]	
	Omega-3 reduces host resistance to *Mycobacterium tuberculosis* [104]	Only experimental data available
Respiratory infections	β-carotene and vitamin E supplementation do not prevent or reduce morbidity associated with pneumonia	Limited data available
	Vitamin D associated with increased risk [80–82]	RCT data are inconsistent

RCT: randomised controlled trial.

Lung cancer

As far as lung cancer is concerned, diets high in fruits and/or vegetables are beneficial, irrespective of smoking habits [123], especially when foods are consumed raw [124]. Dietary fat consumption (total, saturated, monounsaturated and polyunsaturated fat and cholesterol) was not associated with lung cancer risk in a 2002 pooled analysis of prospective studies [125]. In addition, high red meat consumption in heavy smokers increases the risk of lung cancer [126], while high vegetable fat intake may prevent lung cancer [127]. Finally, the Mediterranean dietary pattern is almost consistently associated with reduced lung cancer incidence [128].

Maternal diet during gestation and diet during childhood

An issue of ongoing research is the effect of diet during pregnancy and/or early life nutrient status on lung development and respiratory illness. Lung development is almost complete prior to birth and, following birth, airway changes are in general limited to increases in length

and diameter [129]. On this basis, fetal early life exposures, such as maternal diet, may have disproportionate effects on the development of respiratory disease [129].

Antioxidants

Changes in dietary antioxidant intake during pregnancy may contribute to increases in asthma. Low maternal vitamin E and zinc consumption results in increased asthma-like symptoms, while vitamin E levels during pregnancy are positively associated with post-bronchodilator FEV_1 [130]. However, no associations were observed between children's nutrient status and asthma. In addition, maternal plasma and cord blood selenium concentrations are negatively correlated with wheezing in the first 2 years of life but not in the first 5 years of life [131]. Vitamin D levels are lower in asthmatic children, while vitamin A levels are negatively correlated with asthma severity [132]. Similarly, low vitamin C concentrations are associated with asthma in children [133]. However, increased vitamin C intake during pregnancy was positively associated with wheezing in the first 2 years of life [134]. In a recently published meta-analysis, a maternal diet high in vitamin E was found to be protective in terms of wheezing outcomes [113]. Although the current data provide evidence of an association of antioxidants with childhood asthma, they must be interpreted with caution due to the cross-sectional design of the studies, which cannot establish a causal relationship.

Vitamin D

Few studies have assessed the role of vitamin D in asthma prevention and the data are rather conflicting. Some studies have suggested that maternal dietary intake of vitamin D is negatively associated with asthma or wheeze in early childhood [135]. By contrast, others have observed that high maternal 25(OH)D levels during pregnancy are associated with asthma outcome at 9 years of age [136]. In addition, cord blood levels of vitamin D are negatively associated with childhood wheeze at 15 months, 3 years and 5 years of age, and the risk of respiratory infection at 3 months of age, while no association was found with asthma at 5 years of age [137]. In a meta-analysis of observational studies, vitamin D intake during pregnancy was beneficial in terms of asthma prevention [113]. The inconsistency of these studies may be explained by the findings of Hyppönen *et al.* [138], who demonstrated that a U-shaped and not a linear relationship exists between vitamin D concentrations and IgE levels, suggesting that low or high serum vitamin D is associated with allergic diseases, like asthma.

Limited data are available regarding the role of vitamin D in respiratory infection during infancy. In a prospective birth cohort by Belderbos *et al.* [139], low concentrations of 25(OH)D in cord blood was associated with increased risk of RSV LRTI in the first year of life. More studies are needed in order to draw definite conclusions.

Polyunsaturated fatty acids

Intake of PUFAs during gestation may be related to asthma development. Maternal intake of oily fish or fish oil supplementation has been associated with reduced risk of asthma in offspring, although the association may be limited to asthmatic mothers [140]. In contrast, other studies have reported no benefit of fish oil supplementation during pregnancy in the prevalence of asthma [141]. Increased maternal consumption of omega-3 PUFAs has been associated with reduced wheezing at 2 years of age [142], while supplementation with DHA

in a double-blind placebo RCT resulted in reduced infant respiratory morbidity [143]. It seems that omega-3 PUFA supplementation during gestation may have a protective role in neonatal immune responses through the reduction of cord blood mononuclear cell cytokine responses and, especially, IL-10 [144].

Supplementing the diet of infants with omega-3 fatty acids may exert effects on later respiratory health. Omega-3 supplementation in infants results in a reduction in wheeze at 18 months, a result that is blunted at 3 and 5 years of age [145], while early introduction of fish into the diet (at <9 months of age) has been associated with reduced rates of recurrent wheeze [146]. Similarly, fish consumption between 6 and 12 months of age is associated with fewer wheezing events at 48 months of age [147]. By contrast, others have found no association of fish and cod oil consumption on asthma prevalence at 2 years of age [148].

Although the current evidence supports a link between PUFAs and asthma prevention, more studies are needed to further substantiate the proposed hypothesis.

Discussion

An important aspect of dietary habits, besides the nutrient content of diet, is the cooking method and the process applied to the foods consumed. For example, processed meat (such as bacon and sausage) has a high content of nitrites with important pro-oxidant capacities that may contribute to lung inflammation [149]. Exposure of meat to high temperature results in the formation of heterocyclic amines and the polycyclic aromatic hydrocarbon benzo(a)pyrene, which carry a high mutagenic and potentially carcinogenic effect [150]. Studies have suggested that processed meat intake during pregnancy may increase the risk of wheeze in children [117], while processed meat consumption is associated with worse lung function, a result that is partially reversed by fresh fruit consumption [149]. The data are limited; however, it seems that the manner in which the foods are processed prior to consumption affects the compounds to which the consumer is exposed and should be taken into consideration.

Another important concern regarding the role of diet in respiratory diseases is the potential effect of the individual's genetic variants on the effect of the nutrients consumed. *In vitro* studies have suggested that NSCLC cell lines carrying epidermal growth factor receptor mutations are more responsive to vitamin D treatment compared with those with *Kras* mutations [151]. Interestingly, patients carrying vitamin D receptor *Bsm*I polymorphisms have a significantly reduced TB risk [152, 153], while COPD patients with single-nucleotide polymorphisms in the vitamin D binding gene are more sensitive to vitamin D supplementation [56]. Although gene–environment interactions seem important in the assessment of the role of diet in respiratory diseases, further studies are needed to clarify the effect of the host's genetic background on the effect of dietary habits on lung health.

Conclusion

Accumulated evidence from observational studies implies that diet may be an important cofactor in lung health and disease. However, the published evidence cannot elucidate the temporal association of nutrition and lung disease, mainly due to the cross-sectional nature of the studies and the possible confounding factors that may interfere with the results (*i.e.* lifestyle patterns and tobacco smoke exposure). The published interventional studies provide

inconsistent data and, thus, the clinical relevance and therapeutic potential of the association is not clear. The impact of a "healthy diet" and dietary patterns as a cofactor in lung diseases should be further investigated in order to provide public health policy measures. Diet during gestation or early childhood may have disproportionally greater effects on the development of lung diseases and should be further explored.

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Poverty and health disparities

Valeska Padovese, Raffaele Di Palma and Concetta Mirisola

Poverty deprives individuals of the freedom to satisfy basic needs and rights. The poor are exposed to greater personal and environmental health risks, are less well nourished, are less informed about health, and are less able to access healthcare; they thus have a higher risk of illness and disability.

We reviewed scientific literature and disclosed unpublished data concerning health conditions of migrants, the homeless and Roma people in Europe with particular regard to respiratory conditions, *i.e.* the re-emergence of TB related to the influx of migrants from highly endemic countries; the prevalence of respiratory allergies and acute respiratory infections in migrants, residents and Roma people due to unhealthy environments; and COPD in homeless people related to high nicotine consumption. Furthermore, we discuss public health policies addressing these fragile segments of the population and propose inclusion models.

Poverty is a term that covers a spectrum of material and financial deprivation ranging from low income to relative or absolute poverty. Although generally understood to be related to having too little money, poverty is difficult to define. There is no one standard or definition that can be universally applied. Most definitions are ones that are derived for particular political, fiscal, welfare and other purposes [1].

Poverty deprives individuals of the freedom to satisfy basic needs and rights. This might include freedom to achieve sufficient nutrition, to obtain remedies for treatable diseases or to access health facilities. This lack of freedom prevents individuals from fulfilling their potential, thus leading to a great loss for society and hampering development. Poverty might also be the source of stigmatisation within subgroups of our societies, within national borders and among countries.

The poorest of the poor, around the world, have the worst health. Within countries, the evidence shows that, in general, the lower an individual's socioeconomic position, the worse their health. There is a social gradient in health that runs from the top to the bottom of the socioeconomic spectrum. This is a global phenomenon, seen in low-, middle- and high-income countries [2].

Over the last century, average health status has improved in Europe. However, these gains are not evenly distributed across countries or across social groups within the same country. Poverty is a key factor in explaining poorer levels of health between the most and least

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well-off countries and population groups within the same country. Yet, differences in health also follow a strong social gradient. This reflects an individual's or population group's position in society, which translates into differential access to, and security of, resources such as education, employment and housing, as well as differential levels of participation in civic society and control over life. The poor are exposed to greater personal and environmental health risks, are less well nourished, are less informed about health, and are less able to access healthcare; they thus have a higher risk of illness and disability. Conversely, illness can reduce household savings, lower learning ability, reduce productivity and lead to a diminished quality of life, thereby perpetuating or even increasing poverty in a vicious circle [2].

Human mobile population: bridging the health disparities

Human movements have long been recognised as important factors that can affect health. Early historical relationships between mobility and health, and the attempts to manage or influence these events, were primarily focused on communicable diseases, due to the fear of importing exotic infections from high-prevalence countries.

Migration to the European Union (EU) has increased exponentially during the past two decades. During 2011, there were an estimated 1.7 million immigrants to the EU from countries outside the EU-27. The UK reported the largest number of immigrants (566 044) in 2011, followed by Germany (489 422), Spain (457 649) and Italy (385 793); these four member states together accounted for 60.3% of all immigrants to EU-27 member states. In absolute terms, the largest numbers of non-nationals living in the EU on January 1, 2012, were found in Germany (7.4 million persons), Spain (5.5 million), Italy (4.8 million), the UK (4.8 million) and France (3.8 million) [3].

As the volume and nature of human movement have expanded, interest in the health of mobile populations has increased. The relationships between health and population mobility can be described in terms of two major processes. The first is the process of mobility; the second is that of disparity. Each of these major factors has an intrinsic series of corresponding influences and effects on the health of the traveller and the broader community. Health parameters and outcomes differ widely across and between regions of the world. Large variations persist even among states with similar national statistics in terms of financial and social standards.

Disparity is perhaps the most important factor in the relationship between mobility and health [4]. The movement of people between areas of disparate health indicators, often from the developing or rural world to more developed or urban areas, creates a functional bridge between these differences. In a time of expanding and more rapid travel, there is more movement that results in the bridging of health disparities. Individuals and populations can easily travel between locations or regions where certain diseases are of high prevalence to destinations where the same disease is rare or has been eliminated. TB infection in low-incidence countries is a common presentation of a mobility-associated chronic infectious disease of significant public health importance. In Europe, more than half of all active TB cases occur in foreign-born individuals [5]. TB prevalence in Malta has doubled in the last decade in line with an increase of landings of boat migrants from sub-Saharan Africa (fig. 1). The sharp increase of TB notification cases among boat migrants in Malta, in line with the number of arrivals, which started to be important only in the last decade, has determined a peak in the overall TB prevalence (Chest Clinic, St Luke's Hospital, Valletta, Malta; unpublished data). As a consequence, public health policies have been addressed in an

attempt to control TB spread in Europe; active case finding by radiological screening for TB and contact tracing at the point of entry, targeting specific high-risk groups, has re-emerged as a viable approach [6]. Nevertheless, the arrival of large numbers of migrants from regions where the prevalence of TB is high has resulted in the import of a large burden of latent infection, which can generate future active cases. Migrants from highly endemic areas represent populations at increased risk for reactivation of latent primary infection, which can translate into personal and community health risks requiring non-traditional community-based public health responses. Screening for the disease, providing treatment or reducing the likelihood of outbreak by preventative therapy, isolation and restricted movement is essential in the attempt to manage the population-based risk. In situations where interventions exist for control or elimination of the infection, assessment or screening of mobile populations may need to be considered as part of routine health care for these individuals [7, 8].

Research data from the National Institute for Health, Migration and Poverty (NIHMP) Reception project 2008–2011 in Lampedusa, Italy, confirm that migrants arrive on average healthier than native born persons; this phenomenon is defined as the "healthy immigrant effect" [9]. The analysis of diagnoses collected *via* medical screening of almost 29 000 migrants landing on Lampedusa in the project period revealed that migrants suffer skin conditions related to the sea journey (skin burns and contact dermatitis; 22.1% of the total diagnoses), followed by infectious diseases (scabies, intestinal parasitism and acute respiratory tract infections; 16.8%) and diseases of the genitourinary system (13.3%). Conditions observed in migrants were acute, due to the journey or the time spent in Libyan prisons and rarely of tropical nature (fig. 2). Some clinical conditions observed on arrival (asthenia, skin burns, dehydration, cramps, postural musculoskeletal aches and acute gastritis) are determined by the horrible conditions of the sea journey from Libya, which usually lasts 3–4 days, but occasionally may go on for 6–8 days.

This health advantage decreases over time, and some particular migrant populations are at increased risk of decline in health status and poorer health outcomes. The medical screening of 3000 migrants living in the 10 reception centres in Malta (NIHMP Mare Nostrum project, 2010–2011) documented that migrants living for more than 1 year in the camps were affected by "diseases of poverty" (skin infections, acute and allergic respiratory diseases and diseases of the digestive system), which were related to environmental factors (poor hygienic conditions, overcrowding in the reception centres and dampness) and wrong eating habits [10]. Despite the fact that migrants were screened for TB, a number of those in good health at

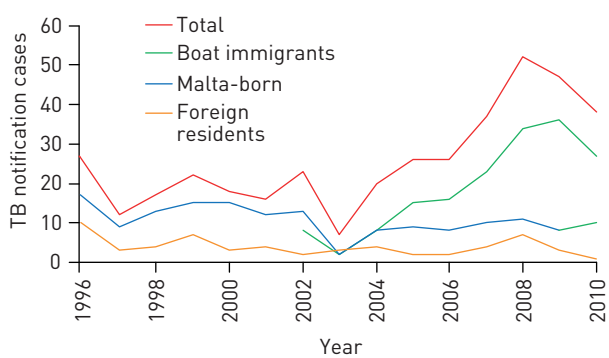

Figure 1. TB notification in Malta, 1996–2010. Data from Brian Farrugia (MEH-Chest Clinic, St Luke's Hospital, Valletta, Malta) with permission.

Figure 2. Human trafficking in the Mediterranean Sea. Image courtesy of National Institute for Health, Migration and Poverty. Published with the permission of Valeska Padovese.

the entry point developed a positive Mantoux test and radiographic changes compatible with TB disease, compared with the chest radiograph at entry; this confirms again that living conditions in reception centres favour TB spread in the migrant community [7].

Research into the impact of migration on health services is increasing in its importance across Europe. In particular, questions remain around how best to provide access to an appropriate quality of healthcare to the growing population of irregular migrants who may not be eligible to access national health services on arrival and the level of healthcare provision afforded to vulnerable groups such as asylum seekers and refugees. The NIHMP in Rome, Italy, offers a model of facilitated access to healthcare systems addressed to fragile populations, foreigners and the destitute (www.inmp.it). The NIHMP staff is composed of professionals in different disciplines and from several countries; integrated work between doctors, nurses, psychologists, anthropologists and cultural mediators allows a holistic and multicultural approach. The analysis of medical records of 46 752 foreign-born individuals seeking medical care at the NIHMP outpatient department in the period 2007–2014 revealed that respiratory conditions are a small percentage (4.9%) out of the total diagnoses, with a prevalence of acute respiratory tract infections and allergies (NIHMP; unpublished data). Migration involves exposure to a new set of pollutants and allergens. Environmental factors and lifestyle in western, industrialised cities seem to be associated with this increased risk. Immigration to allergy-prevalent countries causes more allergies and asthma in immigrants compared with the prevalence of atopy in their countries of origin. The effect is time-dependent and migrants, in general, are more prone to the development of allergies than the local population: early age and longer time spent in the new environment increase the likelihood of developing allergenic symptoms, such as asthma or rhinoconjunctivitis [11]. Further research on possible strategies for primary prevention in high-risk atopic individuals and secondary prevention is needed with the aim of developing guidelines both for populations in developing countries and for immigrants from such countries [12].

Finally, an important consideration in the development and implementation of awareness programmes dealing with health issues in migrants and mobile populations is the necessity to avoid stigmatising and further marginalising groups that may already be discriminated against. The association between infectious or contagious illnesses and identifiable non-native populations can support isolation, impede integration and reduce compliance. Public health interventions, surveillance activities and disease control initiatives for mobile populations will need to be culturally appropriate and paralleled by appropriate communication and public awareness activities.

Homelessness and health

In 2010, RAIS (Red de Apoyo a la Integración Sociolaboral) estimated that 3 million people in Europe were homeless but this is on the increase, with rises recorded in most EU member states, as the economic crisis and austerity policies hurt the most vulnerable. The report "'On the way home': FEANTSA monitoring report on homelessness and homeless policies in Europe" states: "For Greece, Ireland, Italy, Portugal, Spain, and the UK, the crisis was identified as a key driver of increased homelessness in the past 5 years […] Several of the countries most affected by the crisis, such as Greece, Portugal and Spain have experienced dramatic increases in homelessness. Homeless Service providers in Portugal and Spain estimate increases of 25–30% in the demand for homeless services since the onset of the crisis. In Greece, despite a lack of reliable statistical data, there are clear indications of a large and rapid increase in homelessness" [13].

Different factors can affect the susceptibility risk of homelessness: structural (poverty, unemployment, immigration status or housing exclusion), institutional (discharge from institutional living or prison), relationship (leaving family home or domestic violence) or personal (disability/mental illness or drug and alcohol addiction). Whatever the cause, homelessness is synonymous with social exclusion and health inequality. It is also recognised as an independent risk factor for premature mortality.

Homeless people often face significant barriers to medical support. Healthcare usage among homeless people is characterised by unplanned and emergency care. This marginalised group shows a higher risk of chronic diseases and multimorbidity than the general population. Data from the Department of Health in London, UK, show that homeless people, compared with patients who are not homeless, attend accident and emergency departments five times as often, are admitted to hospital 3.2 times as often and stay three times as long, resulting in unscheduled secondary care costs that are eight times higher [14]. Mortality from respiratory infections is seven times greater among homeless people [15]. This is compounded by a high prevalence of chronic respiratory diseases, and high rates of tobacco smoking and illicit drug use. Homeless adults are at greater risk of vaccine-preventable respiratory infections due to a high prevalence of underlying medical conditions and increased transmission risk associated with congregate living in confined shared air spaces [16].

Studies from Germany have shown that more than 90% of homeless people suffer from conditions requiring medical care [17]. Compared with people living in poverty, homeless persons suffer more often from COPD and rate their health considerably lower than the comparison group. Numerous studies have indicated that many variables typical of low socioeconomic status and homelessness (*e.g.* low education, low income, high financial strain and unemployment) are associated with a reduced likelihood of smoking cessation. Worse health behaviour was also reported by a study from Vienna, Austria [18]. Homeless

individuals matched with control subjects smoked more, consumed more alcohol per month, drank alcohol in the morning more often and suffered significantly more often from respiratory disorders (chronic bronchitis and emphysema), which could be related to high nicotine consumption.

Despite medical care facilities for the homeless in some European countries, this population continues to be medically underserved. Many studies indicate that barriers to healthcare exist for the homeless. To improve the health of homeless persons, structural measures are required, such as adequate coverage of basic healthcare needs, equal standards of healthcare for homeless and non-homeless people, cooperation with medical specialists outside the welfare system, and training for medical personnel about the particular needs of homeless people.

Ethnic minorities: the case of Roma people

Health disparities are particularly troublesome among ethnic minorities, such as the Roma. The EU acknowledges that the Roma people are one of the most marginalised social groups, living in very poor conditions with low housing standards. Furthermore, stereotypes, prejudices and discrimination, combined with an attitude of self-exclusion, halt real integration and greatly impact on the resort to socio-healthcare services [19].

Roma children are more likely to be underweight than other children and suffer from respiratory diseases with a higher incidence of asthma symptoms, which could lead to a worse asthma prognosis in later years. Moreover, the prevalence of asthma and the incidence of asthma symptoms vary significantly according to the settlement of origin and the state of the housing in which the child lives [20]. *The Lancet* published an article in 2010 stressing the precarious living conditions of Roma people in Italy, which equate those of Brazilian favelas. In the capital of Italy, an estimated 24% of Roma children are malnourished and 25% are born underweight. 20% of Roma children have bronchitis or pneumonia [21].

A recent survey conducted in Milan, Italy, evidences a more fragile health situation for Roma and Sinti people if compared with other groups, including the overall group of migrants, due to a lower sociocultural level (25% have never attended school; only 16% declare working) and more critical living conditions in their camps. Smoking is very common habit: 56% of individuals aged 12 years or older declare smoking (70% of whom smoke more than 10 cigarettes per day). As for adults, medical visits are mainly due to either respiratory apparatus-related diseases (21%; 60% among minors under the age of 14 years) or due to trauma (13%) [22].

From the few available data, life expectancy of Roma people, combined with higher levels of child mortality, reduces their expectations. Specifically, the estimated life expectancy of Roma is 10 years shorter than that of the general population. Living stateless and undocumented, many Roma are effectively cut off from society with little opportunity for legitimate work, healthcare or normal housing. A study on social and health conditions of Roma people in Bosnia and Herzegovina demonstrated that living conditions and access barriers to healthcare provision contribute to an increased prevalence of chronic diseases. Comparing the prevalence of these diseases in Roma with those of the general population, the rates of morbidity were significantly higher among Roma [23]. One of the few sources providing data about health conditions and education among the Roma is the report "The health situation of the Roma communities" [24], which indicates, for instance, that 15% of Roma participants over the age of 14 years who have finished post-secondary school suffer from chronic

diseases, compared to twice that many (32%) among those who have no formal education. Educational factors are recognised as having a significant impact on basic health indicators such as perceived health status.

The Roma also have inadequate access to prevention services: over 25% of Roma children do not adhere to vaccination schedules. As a consequence, there seems to be increased incidence of many classic epidemic diseases as well as more newly identified infections. Mycobacterial infection is reported to be more common among Roma than in other populations, and increasing at a faster rate.

In this context, studies have revealed the need to emphasise more strongly social inequalities and to promote multisectorial policies (including health) that aim to reduce poverty by improving educational levels, to reduce the health disparities among the Roma communities and other ethnic minorities and vulnerable groups [25]. The lack of prevalence data and analysis of determinants is a detriment to the health of the Roma populations. Although the literature overall is fragmentary, the most striking finding is the almost complete absence of research on noncommunicable diseases, probably due to difficulties of undertaking research in marginalised populations with well-developed sets of health beliefs [25].

The priority areas identified by the communities themselves concern nutrition and personal hygiene; genetic risks related to frequent intermarriage (*e.g.* a high rate of disabled children among those born from Khorakhanè families (Roma Muslims from Kosovo) compared with among those born in Roma families in Serbian and of the Orthodox Christian religion); health risks derived from the burning of refuse in poorly ventilated areas (very common practice among Romanian Roma). Exposure to biomass smoke increases the risk of ALRI in childhood, particularly pneumonia.

Conclusion

In most nations today, inequality, the gap between the rich and the poor, is quite high and often widening. The causes are numerous, including a lack of individual responsibility, bad government policy, exploitation by people and businesses, or some combination of these and other factors. Poverty is a silent killer and despite the scale of this ongoing catastrophe, it rarely manages to achieve headline coverage. Direct effects of poverty are measurable by the increased prevalence of certain diseases and mortality in the population concerned. Education is today the most reliable indicator to represent the social inequalities in life and in regard to mortality.

What can be done? We must find a modality of action, in addition to the political procedure, which remains the central issue. It is necessary to give visibility and a social substance to the dispersion of inequality, addressing research toward marginalised people in order to implement social inclusion and find specific solutions in the local context.

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Chapter 19

Study design: features of non-experimental studies

Vittoria Colamesta[1] and Riccardo Pistelli[2]

Epidemiological research is carried out by both experimental and non-experimental study designs. Experimental studies are rarely used in epidemiology. These studies are performed under the control of the investigator, who can assign treatment (exposure) to patients *via* randomisation in order to achieve quite similar experimental subgroups and avoid bias, due to the effect of unbalanced factors. However, an experimental study often cannot be carried out in all areas of research, epidemiology being one, for technical or ethical reasons.

In non-experimental studies, the investigator purely acts as an observer. They do not control the exposures, only the selection of included subjects and the proper treatment of confounding factors. There are several non-experimental study designs, the most popular of which will be described in this chapter, along with their specific targets, strengths and weaknesses. For each design, an example from the current literature will be used to analyse some methodological issues.

Epidemiological studies can have either a non-experimental or an experimental design. In non-experimental studies, better known as observational studies, the investigator is only an observer and does not assign any treatment. The association between outcome and exposure that is demonstrated in these studies, by far the most commonly used studies in epidemiological research, can only suggest a causal relationship [1]. The experimental design, if ethically and technically possible, aims at reducing the effects of extraneous factors on outcomes by a randomised allocation scheme, which is applied to the assignment of interventions. In these studies, the exposure (intervention) can be assigned to a patient and the relationship between exposure and outcome can be interpreted in terms of causality. Randomised controlled trials are typical examples of experimental studies for clinical research, whereas field trials and community interventions, although only seldom performed, are typical examples of experimental studies for epidemiological research. Experimental studies are beyond the aims of this chapter. Herein, we will only discuss observational studies.

Observational studies can generally be carried out at a lower cost than experimental studies and may be the only available choice when it is not possible to carry out an experimental study for ethical or technical reasons. Observational studies can be performed in many areas and include several study designs, the most popular of which are: cohort, case–control, cross-sectional and ecological. The main characteristics of these studies are summarised in table 1.

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The quality of the methods and the efficacy of the reports from observational research may be evaluated by standardised instruments. These are well known by the authors of systematic reviews and meta-analytic publications.

The methodological quality of nonrandomised studies, including cohort and case–control designs, can be evaluated using the Newcastle-Ottawa Scale [3]. A study is evaluated based on three perspectives: 1) the selection of the study groups; 2) the comparability of the groups; and 3) the ascertainment of exposure and outcome for case–control and cohort studies, respectively. The authors of the Newcastle-Ottawa Scale developed a "star system" to identify studies of "high" quality, in order to avoid distortion of the summary effect estimate due to "low" quality studies that were included in the panel [3]. The STROBE statement (Strengthening The Reporting of Observational Studies In Epidemiology) is a guide to

Table 1. Main characteristics of observational studies

Study design	Strengths	Weaknesses	Principal results[#]
Cohort	Clear definition of the cohorts Knowledge of exposure and disease timing Good reliability of data Possibility to study multiple outcomes	Follow-up of cohorts required (follow-up bias) Expensive and time consuming Large sample size required Not suitable for rare diseases	Calculation of incidence rate and relative risk
Case–control	Short time period and cheap Suitable for rare diseases Small sample size	Possible selection bias Questionable reliability of data	Calculation of the odds ratio
Cross-sectional	Easy and cheap to realise Follow-up not needed Measure of prevalent cases Suitable for multiple or rare exposures Useful to analyse the trends of a health problem with repeated survey Coexisting descriptive and analytical section	Not suitable for rare diseases Weakness in establishing a causal relationship between exposure and outcome Possible selection and recall bias Possible length-biased sampling	Calculation of prevalence and odds ratio
Ecological	Possible use of current data Definition of frequency of disease and level of exposure at group level	Possible use of proxy measures for exposure and disease Inadequate control of confounding	Evaluation of rates in specific groups Calculation of association at group level

[#]: relative risk and odds ratio are measures of association in epidemiology. If meaningful prevalence or incidence rates are available, it is possible to directly calculate the relative risk, otherwise the odds ratio provides a valid effect measure. Relative risk and odds ratio are mainly influenced by two factors: the initial risk of an event and the strength of the association between exposure and outcome [2].

standardise reporting of observational research and includes a checklist of 22 items that can be applied to cohort, case–control or cross-sectional studies [4]. 18 items are common to cohort, case–control and cross-sectional studies, while four items are specific for each study design. This checklist is not intended as a method to evaluate the quality of studies included in a systematic review [4].

Cohort studies

Cohort studies are also called follow-up or incidence studies [1]. In a cohort study the investigator can measure, at the end of the study, the incidence rate of the outcome considered (*e.g.* the onset of a disease, the relapse of a disease or the death of patients) in a population or in a selected group of patients or individuals. The investigator acts purely as an observer, recording the new occurrences of the outcome in the subjects included in the study and classified as exposed or not exposed to a specific factor. The inclusion of subjects in the cohort is determined by the outcome studied. Each subject is classified into a subgroup, according to their individual exposure so the investigator can compare the incidence rate in the exposed and non-exposed group. In the cohort study design, unlike the case–control design, it is possible to study multiple outcomes.

Cohort studies can be prospective or retrospective (historical cohort). In the prospective cohort, data are collected during the ongoing follow-up period at the time of their occurrence, while in the retrospective cohort data are collected with reference to the time of their occurrence in the past up to the current time. Ideally, in a prospective study, at the beginning of the study the individuals included in the cohort do not have the disease or whichever clinical situation has been selected as the outcome. The subjects are followed during the study period and defined as affected or not affected by the specific outcome well after they have been divided into the exposed and unexposed group. In a cohort, the included individuals can finish the study, be lost to follow-up or die during the study. Whatever the case, each subject contributes their own period of observation. Therefore, a weakness of this study design is the possibility of lost to follow-up bias. A cohort study primarily aims at measuring the incidence of an outcome by computing the cumulative incidence or incidence rate [5].

The cumulative incidence (or incidence proportion or incidence risk) is expressed as a ratio with the number of occurrences of the outcome as the numerator and the number of individuals at risk to develop the outcome included in the study at the beginning of the follow-up period as the denominator. We can also calculate the ratio of two incidence risks (incidence risk ratio; IRR). The incidence rate (or incidence density or person-time incidence) is calculated using cumulative incidence as the numerator and person-time as the denominator. Person-time is calculated by adding together all time periods that individuals are at risk of developing the outcome for all of the individuals included in the study. The incidence rate is the measure of risk that can be used when studying a dynamic cohort is characterised by a varying composition over time and includes subjects that contribute different times of observation [6].

The association between exposure and outcome in the cohort study is usually expressed as relative risk, the ratio of the incidence risk (absolute risk) in the exposed and non-exposed subjects. We can calculate the difference of incidence risk (risk difference between exposed and non-exposed subjects), from which it is possible to calculate the number of occurrences we may avoid in a time period, by reducing the level of exposure in a population. We can also calculate the proportion of events in an exposed population that can be avoided by removing

a specific risk factor (attributable risk). An alternative expression of relative risk is hazard ratio, the ratio of incidence rates in the exposed and non-exposed subjects [5].

An example of this study design is the study conducted by GENUNEIT *et al.* [7] on the association between smoking and asthma or wheeze during adolescence. The authors conducted a large population-based cohort study in two German cities (Dresden and Munich). At baseline, 6399 children aged 9–11 years were enrolled as participants in phase II of the International Study of Asthma and Allergies in Childhood (ISAAC). The same subjects were requested to participate in a new survey, 7 years after the previous one. Only 3785 subjects from the original cohort were traced and agreed to fill in a questionnaire and, after further exclusions due to criteria related to the design of the study, the final cohort included only 2936 (46%) subjects. The authors recognised some important differences (*e.g.* sex and socioeconomic status) between the subjects studied at baseline and those included in the cohort. These differences do not compromise the internal validity of the study but may be relevant for the inference of results to the general population. A second limitation of the study derives from the possible misclassification of exposure to active or passive smoking, which was assessed only by using answers to a questionnaire. Moreover, the study was based on two observations during the study period but active smoking was only evaluated in the second survey; thus, it was impossible to define exactly the temporal relationship between onset of illness and exposure to cigarette smoke. Thus, it was impossible to define exactly the temporal relationship between onset of illness and exposure to cigarette smoke, which is the assumption typical of the cohort design (exposure prior to the outcome) may not have been respected in this study.While recognising all these limitations, the authors calculated the IRR for incident wheeze between active smokers and nonsmokers, adjusted for potential confounders using a modified Poisson regression approach. They found a significantly increased adjusted IRR towards developing wheeze or asthma in active smokers, and observed a dose-dependent association with the duration and intensity of active smoking [7].

Case–control studies

For rare diseases, a cohort study is not practical, thus the case–control design may be a useful alternative. In a case–control study, a group of people are selected on the basis of their disease status. The source population identified in a case–control study may represent a hypothetical study population for a cohort study. If cases are identified as a representative sample of all cases in a defined population and the controls are randomly sampled from the same population, the study is called a population-based or primary base case–control study. By contrast, an investigation in which it is not possible to identify the source population in order to select random controls, and other methods must be used to select controls, is called a secondary base case–control study. Those in the source population who develop the disease being studied can be included as cases in a case–control study. However, it is not necessary to include all cases from the source population in the study it may be enough to include only a random sample, provided that the sampling procedure is independent from the exposure being studied. The selection of controls, the most important issue in this study design, depends on the definition of the source population. Ideally, controls should be selected from the same population as cases and independently from their exposure status. When it is not possible to select controls from the source population, controls can be chosen using one of following methods: neighbourhood controls (sampling of residences), random-digit telephone dialling, hospital- or clinic-based controls, patients with other diseases not related to the exposure being studied, friends of controls or dead controls. The most important issues while carrying out subject selection in a case–control study are: the representativeness of

cases and controls, the comparability of information accuracy between the two groups, and the number of controls selected for each case.

A case–control study can be prone to recall bias. In fact, if the information about exposure is obtained during an interview, cases informed about their disease status usually report the information about exposure more accurately than controls. Another limitation of this study design is the ambiguous temporal sequence between exposure and disease. The results of a case–control study are usually reported as odds ratios (ORs), *i.e.* the odds of being exposed among cases divided by the odds of being exposed among controls. This ratio is an estimate of the relative risk and measures the strength of association between the exposure (risk factor) and diseases being studied [8].

There are several variants of the basic case–control study. A nested case–control study is an investigation conducted within a cohort study, in which the population is a cohort and the cases that occur in the cohort are compared with the remaining healthy subjects of the same cohort. The case–cohort study is similar to the nested case–control study. In this study design the source population is a cohort in which each included subject has an equal probability of being included as a control because controls are selected from the whole cohort, while in a case–control study controls are chosen by a different sample of no cases. Another variant of the case–control design is the case–crossover study. In this study, each subject is observed for one or more pre- and post-disease time period in order to obtain the "control" period for each case. Therefore, the exposure status of a subject at the time of disease onset is compared with the exposure status in the control periods in the same subject [8]. This study design may be useful to analyse the effect of short-term exposures characterised by transient effects on the risk of developing acute disease, *e.g.* asthma or COPD exacerbation [9]. This design is also used in environmental epidemiology to analyse the effect of air pollution on human health [10].

A particular variant of the case–control design is the prevalent case–control study. This is based on prevalent cases instead of incidence cases when it is not possible to select only incident cases (*e.g.* chronic conditions).

The study by John *et al.* [11] reports results obtained using this study design. The authors performed a case–control study to investigate tobacco stains on fingers as a marker of tobacco-related disease to find behavioural and environmental characteristics associated with the stains. This study was carried out in a 180-bed Swiss community hospital between March 2006 and January 2010. It included current smokers admitted to the departments of intensive care, internal medicine or surgery, regardless of the diagnosis at admission. They consecutively enrolled cases defined as patients having tobacco stains on fingers. Controls were selected randomly from the same population to satisfy the matching criteria (age, sex, height and pack-years). A history of smoking-related cancer, ischaemic heart disease, peripheral arterial disease, stroke and COPD confirmed by lung function test were collected from both groups. In addition, alcohol intake, mental disorders and smoking habit were recorded. The authors found that 84% of cases had a history of smoking-related diseases. In a multivariate analysis, harmful alcohol use, but not smoking-related diseases, was strongly associated with tobacco-stained fingers. This study suggests a possible link between tobacco-stained fingers and harmful alcohol intake. One of the limitations of this study was that the investigators were not blinded to case or control status, which may have influenced the clinical interview of included subjects. Furthermore, the authors selected their controls from the population of patients in the hospital, in this way increasing their probability of controls

being affected by the same diseases as cases and artificially decreasing the strength of the association between exposure and disease.

Cross-sectional studies

A cross-sectional study allows investigators to "take a picture" of all the included individuals or a representative sample of a population at a particular time, without taking into account exposure or disease status. This design can also be used to investigate the practices, attitudes, knowledge and beliefs of a specific population while also obtaining information by, for example, the use of questionnaires or physical and laboratory examinations. Cases included in this study design are prevalent, not incident, at the time of study. This type of study may investigate the frequency of both acute and chronic diseases but, since the prevalence measured in a cross-sectional survey is an underestimation of the real occurrence of an acute disease in a population, a cross-sectional design is only appropriate to estimate the frequency of chronic diseases. In any case, a bias of this study design, often called length-biased sampling, is overrepresentation of cases with a long duration of illness and under-representation of cases with a short duration of disease [1].

A cross-sectional study can include a descriptive and analytical section. The descriptive section includes the description of the disease distribution in the study population according to characteristics of subjects, place and time (age, sex, civil status, citizenship, region, country, year, week, *etc.*). In this section, the study should respond mainly to the questions: who, where and when. In the analytical section, the investigator attempts to demonstrate a possible association between exposures and disease, according to the hypothesis that the investigator wants to study. Thus, the subjects are divided into exposed and not exposed, ill and not ill. In this design, it is difficult to establish the exact timing of events because prevalent rather than incident cases are recorded and the direction of time is not taken into account. In a cross-sectional study, the study group is defined using probabilistic sampling methods and individuals are classified as: exposed with disease, exposed without disease, not exposed with disease, and not exposed without disease. The prevalence of exposure in those with the disease is compared with the prevalence of exposure in those without the disease. The strength of the association between exposure and disease is calculated as the OR. A cross-sectional study is usually performed to estimate the prevalence of a health problem in a population. It may also be reported as a prevalence study. However, the cross-sectional design can also be applied to analyse the trends of a health problem with repeated surveys in the same population. This application of the cross-sectional study is usually known as a trend study [12]. A study that groups some repeated measures at specific time intervals from the same (usually small) sample over a long period (panel study) is particularly relevant in environmental epidemiology.

The study by CHOUDHARY *et al.* [13] is an example of a cross-sectional study. The study assessed the prevalence and clinical characteristics of pulmonary hypertension in African-Americans. The authors performed this study in 3282 patients from the larger Jackson Heart Study cohort. All patients received Doppler echocardiography and had their trans-tricuspid flow measured to estimate pulmonary systolic pressure. The authors found that the prevalence of pulmonary hypertension in African-Americans was 6.8% with a higher age-adjusted prevalence in females. Age, obesity, high arterial pressure, diabetes, obstructive or restrictive pulmonary function profiles, and severe mitral or aortic disease were associated with an increased prevalence of pulmonary hypertension. The age- and sex-adjusted prevalence ratio of pulmonary hypertension increased significantly with left atrial diameter

index and left ventricular ejection fraction <50%. This study estimated the prevalence of pulmonary hypertension in African-Americans and highlighted many factors associated with an increased prevalence of the disease. However, the design of the study doesn't allow the causes of pulmonary hypertension to be established [13].

Ecological studies

In ecological studies the units of observation are not individuals but groups of persons, *e.g.* schools, factories, cities, countries or nations. This study design is also called an aggregate study and is useful to compare the incidence rate between specific groups. Usually, an overall index measures the exposure of individuals in a group [1]. The ecological measures can be: aggregate (means or proportions), environmental (physical characteristics of the place) or global (features of groups or organisations). When exposure varies across individuals in each group, the between group strength of association of exposure and disease does not reflect the strength of association at the individual level. In fact, the major limitation of this study design is the ecological bias (ecological fallacy): the ecological associations can differ from the corresponding individual associations [14]. Another limitation, which may produce biased estimates of the strength of association, is the choice of proxy measures for exposure and disease commonly used in this type of study. Moreover, available data in an ecological study are usually not adequate in order to adjust the estimates of association, at least for the most plausible confounding factors [1]. With all these limitations in mind, ecological studies can often be performed with currently available data, thus saving money and time. The results of these studies are mainly considered as useful generators of ideas and hypotheses, which must be checked in future studies that have a different and more powerful design.

It is worth citing here two studies that were designed as surveys to evaluate the prevalence of diseases that are common in many areas of the world, but which also intended to generate ideas about factors that could explain the prevalence differences between areas by analysing data at the ecological level. ISAAC is an epidemiological investigation, with two global phases within a 7-year period, which aims to describe the prevalence and severity of asthma, rhinitis and eczema in children from two age groups (13–14 years and 6–7 years). ISAAC also aims to make comparisons within and between countries, assess future trends in the prevalence and severity of these diseases, and provide a framework of ideas and hypotheses for further research in genetics, lifestyle, and environmental and medical care [15]. The European Community Respiratory Health Survey (ECRHS) is another epidemiological study into asthma and COPD that includes adults. The study was designed with a two-step approach (screening questionnaire and clinical evaluation) and two phases have been performed at a global level 7 years apart. Strong ecological correlations between asthma prevalence and other conditions measured in the same areas by the ISAAC and ECRHS studies have been published [16]. Unfortunately, the ideas generated in the ecological analysis are still waiting for an appropriate study to demonstrate their validity.

Conclusion

Each epidemiological study design has its own targets, strengths and limits, which the investigator must be aware of while performing the study. Before starting a study it is worth choosing the most appropriate design in order to answer the study question. The precise definition of outcomes and exposures may improve the ability to obtain statistically significant results, but biases deriving from a poor quality study design or from some wrong

sampling procedures may prevent the investigator from obtaining meaningful results. Of course, the analysis of data collected in each study should be coherent with the study design and, whenever possible, take into account the distortion of results by some confounding factors that, by definition, are unavoidable in the design of observational studies. Studies derived from observational research will increase their diffusion in the literature in the coming years and the common reader of medical journals should be prepared to critically evaluate those papers, as well as the reports of randomised controlled trials.

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Questionnaires and lung function

Francesco Pistelli[1] and Sara Maio[2]

Questionnaires and lung function testing are important instruments of measurement in respiratory epidemiology.

Questionnaires allow the investigation of large population samples through the collection of subjective data. Their basic methodological requirements are validity, reliability and bias. The first standardised respiratory questionnaire was developed by the British Medical Research Council in the 1950s, and was the basis of subsequent questionnaires developed in Europe and the USA. More recently, *ad hoc* questionnaires for specific studies have been produced, even though existing validated questionnaires still appear to be largely used.

Lung function testing has several applications in respiratory epidemiology. Standardised procedures have been developed to minimise variability of lung function testing measurements, and updated reference equations have been derived to improve interpretation of results. Spirometry is the most frequently used test in population-based studies but other tests, including diffusing capacity or methacholine challenge test, have been shown to be applicable in respiratory epidemiology.

Questionnaires and lung function testing are among the most important instruments of measurement in respiratory epidemiology allowing collection of subjective and objective data, respectively.

Questionnaires are a convenient tool to investigate large population samples due to low cost, ease of use for the investigator, and good compliance of the investigated subject. Questionnaires need to satisfy methodological requirements to guarantee the accuracy of the collected data.

Lung function testing allows lung volumes and other indices to be measured, thus providing an objective assessment of most respiratory diseases. They are also recognised as a measure of global health, predicting all-cause mortality. Lung function testing must be based on equipment and protocols that meet guideline recommendations in order to acquire accurate data, and the interpretation of the obtained results should be standardised to be comparable from one study to another. Moreover, unlike clinical studies, epidemiological surveys often include large groups of "healthy" or asymptomatic individuals, allowing methodological and

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technical aspects to be explored through analyses of measurements that are not affected by pathological conditions.

This chapter aims to describe the general features of respiratory questionnaires and lung function testing, as well as their use in population-based studies.

Questionnaires

Since the classic paper by COCHRANE *et al.* [1], questionnaires have become a recommended tool of investigation in both clinical and epidemiological studies. Questionnaires consist of a list of questions that can obtain responses best describing the subjective real situation of an individual. To efficiently collect specific information, the subject being interviewed must be aware of what information is searched and recognise it in the wording of the question [2].

Important methodological features of questionnaires are validity, reliability (or reproducibility) and bias [3, 4]. Validity refers to the degree to which the questionnaire is actually measuring what it resolves to measure. Reliability refers to the degree of stability exhibited when the questionnaire is repeated under identical conditions. Bias is the deviation of results from the truth, due to intrusion of unplanned or unwanted influence; it may reduce the degree of validity and reliability, which may be quantified.

Validity is assessed by comparing the results of a questionnaire with separate, independent measurements used as gold standard (*e.g.* lung function testing and physical examination), and is quantified as sensitivity and specificity. Sensitivity is the proportion of the truly diseased subjects found to be diseased using the questionnaire (true positive); specificity is the proportion of the truly healthy subjects found to be healthy using the questionnaire (true negative). A questionnaire must have the best possible sensitivity and specificity; usually, when sensitivity increases specificity decreases and *vice versa*.

Reliability is assessed by the agreement of responses to the same questionnaire administered at least twice to the same individuals, under conditions that are assumed to have remained the same between administrations. It is quantified by consistency, *i.e.* the proportion of subjects who provide the same answers on different occasions.

Sources of potential bias are related to the design of the questionnaire, as well as to the type of administration. Examples of bias include "observer bias" (*i.e.* qualitative influence on the answers due to the method of administration of the interviewer), "social desirability bias" (*i.e.* under reporting of socially undesirable information), "training effect bias" (*i.e.* under or over reporting as a result of repeated administrations), "recall bias" (*i.e.* differences in the accuracy of the recollection by study participants regarding events from the past), or "information bias" (*i.e.* misclassification of the level of exposure and/or of the disease). Moreover, different wording, sequence of the questions, or inappropriate translation may cause different answers to be obtained [5].

The development of a questionnaire begins with a decision about what information is needed, proceeds through the design of the questions, and is completed by standardisation [5]. This is a set of strategies that aim to limit bias, thus maximising validity and reliability. Examples of strategies for standardisations include: 1) writing questions as clearly and unambiguously as possible; 2) asking variables of interest in different ways so not relying on one question;

3) instructing interviewers on administration protocols; and 4) pretesting the questionnaire to different groups of respondents [3].

Questionnaires in respiratory epidemiology

Several questionnaires used in respiratory epidemiological studies have been validated and published. The first standardised questionnaires were developed in the 1960s to 1970s, when the main research focus was on chronic bronchitis, emphysema and chronic airway obstruction [2, 6]. In the mid-1980s, new questionnaires were developed that mainly focused on asthma, both in the general population and in certain occupations [2]. Finally, due to the increased frequency of nasal allergies, new questions on upper airway disorders were included [2].

The most commonly used questionnaires on respiratory symptoms and risk factors for COPD and asthma are listed in table 1. For the sake of completeness, table 1 includes questionnaires that have been developed in past years and are recommended for clinical purposes by guidelines on COPD and asthma management.

Historical background

The first standardised respiratory questionnaire was developed by the British Medical Research Council (MRC) in the 1950s [17] to investigate the epidemiology of chronic bronchitis, chronic airway obstruction and some of the correlated risk factors. It was first published in 1960 and was extensively modified in 1986 [4, 8]. The British MRC questionnaire was a milestone in the development of a standardised instrument for the diagnosis of chronic bronchitis and, when used properly, has been shown to be unbiased by interviewers and method of administration in epidemiological surveys [18].

Table 1. Most commonly used questionnaires on respiratory symptoms and risk factors for COPD and asthma

Disease	Questionnaire	Acronym	Year	[Ref.]
COPD	American Thoracic Society and Division of Lung Disease of the National Institute of Health questionnaire	ATS-DLD-78-adult	1978	[7]
	British Medical Research Council questionnaire	BMRC	1986	[8]
	European Coal and Steel Community questionnaire	ECSC	1987	[9]
	COPD Control Questionnaire[#]	CCQ	2003	[10]
	COPD Assessment Test[#]	CAT	2009	[11]
Asthma	International Union Against Tuberculosis and Lung Disease questionnaire	IUATLD	1984	[12]
	European Community Respiratory Health Survey questionnaire	ECRHS	1994	[13]
	Asthma Control Questionnaire[#]	ACQ	1999	[14]
	Asthma Control Test[#]	ACT	2006	[15]
	Control of Allergic Rhinitis and Asthma Test	CARAT	2010	[16]

[#]: respiratory questionnaires suggested by international guidelines for clinical purposes.

The respiratory questionnaires developed in Europe and the USA in subsequent years were based on the British MRC questionnaire [4, 6]. In Europe in 1962, the first version of the European Coal and Steel Community questionnaire (ECSC) on respiratory symptoms was produced for occupational epidemiological studies [19]; the most commonly used version is the one modified in 1987 [9]. In the USA in 1971, the Division of Lung Diseases (DLD) of the National Heart and Lung Institute (NHLI) produced the NHLI questionnaire [20]. In 1974, the American Thoracic Society (ATS), together with the DLD, further developed the NHLI questionnaire into the "Questionnaire for respiratory diseases" (ATS-DLD-78), which was recommended for use in epidemiological research [7]. In 1976, in the framework of the Tucson Epidemiologic Study on obstructive lung disease, a newly designed, self-administered questionnaire was developed and validated; the Arizona questionnaire [21].

A modified NHLI questionnaire was developed by the Italian National Research Council (CNR) Special Project on chronic obstructive lung disease (the CNR questionnaire) to collect data on asthma and COPD symptoms/diseases and risk factors. This was the largest prospective population-based study conducted in northern and central Italy in the 1980s to 1990 [22, 23].

In order to find the most valid combination of questions on symptoms identifying asthmatic subjects, the International Union Against Tuberculosis and Lung Diseases (IUATLD) produced the original IUATLD "Bronchial Symptoms Questionnaire" in 1984 [12] and a revised, shorter version in 1986 [24].

Two other standard questionnaires were developed in the 1990s within the European Community Respiratory Health Survey (ECRHS) [13] and the International Study of Asthma and Allergies in Childhood (ISAAC) [25]. The questionnaires included extended items on asthma, asthma-like symptoms and allergic rhinitis. Questions mainly addressed respiratory symptoms, such as attacks of shortness of breath, wheezing, nocturnal cough and chest tightness, while investigated risk factors were the use of medicines for asthma and indoor environmental conditions. Questions on asthma and asthma-like symptoms were taken from the 1986 IUATLD questionnaire, while those on chronic cough and phlegm were from the British MRC/ESCS questionnaires [2].

Recent respiratory questionnaires

A Medline search conducted in April 2014 revealed that, in the past 14 years, questionnaires to assess respiratory symptoms/diseases have been frequently mentioned in papers on epidemiological studies, in particular in those on asthma (table 2). In many cases new, *ad hoc* questionnaires for specific studies were produced, even though existing validated questionnaires appear to still be commonly used. For example, in 2001–2006 the international Burden of Obstructive Lung Disease (BOLD) project developed a standardised protocol to be implemented in a number of countries throughout the world, which aimed to obtain information about the prevalence and burden of COPD [26]. A core questionnaire including sections taken from the ATS-DLD-78, the ECRHS questionnaires and the questionnaire used in the US Lung Health study [27] was produced. It also included the 12-Item Short Form Health Survey (SF-12), a generic measurement of health status [28]. In addition to the core questionnaire, centres participating in the BOLD study added additional questionnaire items reflecting factors either that were unique or of particular interest to the local investigators. The BOLD questionnaire has also been used in the Latin American Project

Table 2. Use of questionnaires in respiratory epidemiology from 2000 to 2014, according to a Medline search conducted in April 2014

Search no.	Search terms	Retrieved references
1	''Epidemiology'' AND ''Respiratory questionnaire''	4630 (100)
2	AND ''Asthma''	1871 (40)
3	AND ''Asthma diagnosis''	1297 (28)
4	AND ''Asthma symptoms''	1653 (36)
5	AND ''COPD''	605 (13)
6	AND ''COPD diagnosis''	461 (10)
7	AND ''COPD symptoms''	526 (11)
8	AND ''Allergic rhinitis''	348 (8)
9	AND ''Allergic rhinitis diagnosis''	228 (5)
10	AND ''Allergic rhinitis symptoms''	301 (7)

Data are presented as n (%). Search no. 2–10 includes the terms from search no. 1 and the additional terms.

for the Investigation of Obstructive Lung Disease (PLATINO), which was performed in five Latin American countries [29].

Within the European Concerted Action entitled "Epidemiological surveys on COPD in different European Countries: prevalence rates and relationship to host and environmental risk factors (CA-COPD)" [30], comparison among different datasets was limited by the use of either modified versions of standard questionnaires or specially designed questionnaires in the different European respiratory studies involved in the project [4, 31, 32]. Therefore, it was decided to collect questions from the questionnaires used in the various analysed respiratory studies and from the most widely used European and US questionnaires, in order to produce a "Compendium of Respiratory Standard Questionnaires for Adults (CORSQ)" [4, 33]. This covers 18 topics, from general information and early life events through environmental risk factors to respiratory symptoms and diseases. The aim was to make a synthetic reference, including proposed or validated standard questions, available that could be used when planning new epidemiological respiratory surveys [4, 34].

In the past decade, the evaluation of quality of life (QoL) has become an important outcome measure in respiratory research. Health-related QoL is evaluated through instruments that assess physical, social and psychological domains [35], and the patient's perception of the impact of these impairments on their QoL [36]. Both generic QoL instruments for any population and disease-specific instruments for patients have been developed [35]. The St George's Respiratory Questionnaire was designed in 1991 to measure health impairment and perceived well-being associated with airways disease in adults, in particular asthma and COPD [37]. It is a validated instrument that exists in 73 languages, and includes 50 items organised into three areas: symptoms, activities and impacts.

Some other disease-specific validated questionnaires on QoL are still to be mentioned. The original version of the Chronic Respiratory Questionnaire (CRQ) includes 20 items, asking about the level of impairment in the domains of dyspnoea, fatigue, emotional function and the patient's feeling of control over the disease [38]. The Asthma Quality of Life Questionnaire-Standardized (AQLQ-S) is a 32-item instrument that targets adults and is based on four domains: symptoms, activity limitations, emotional function and exposure to

environmental stimuli [39]. The strengths of the AQLQ-S include the reliability of its total score, its responsiveness, and its widespread use and availability in more than 20 languages [39]. The Rhinasthma questionnaire was developed to be used in clinical settings, in adult patients suffering from rhinitis and/or asthma [40]. It includes 30 items related to the impact of allergic diseases on QoL.

In past years, simple, short respiratory questionnaires have been developed and validated for use in clinical practice, and have been recommended by international guidelines for standardised management and care of respiratory diseases. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) guidelines [41] reported that two short comprehensive measures assessing COPD symptoms are suitable: the COPD Assessment Test (CAT) and the CCQ. The CAT is an eight-item one-dimensional measure of health status impairment in COPD covering the following aspects: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. The CAT was developed to be applicable worldwide and validated translations are available [11]. The CCQ is a 10-item self-administered questionnaire developed to measure clinical control in COPD patients within three domains: symptoms, functional and mental state. It has been validated and is available in several languages [10].

The Global Initiative for Asthma (GINA) guidelines [42] reported that questionnaires to assess the control of asthma are available and useful not only in research but also in patient care. They have the potential to improve the assessment of asthma control providing an objective reproducible measure, but their clinical value has yet to be demonstrated [42]. Of these questionnaires the two main ones are the Asthma Control Test (ACT) questionnaire and the Asthma Control Questionnaire (ACQ). The ACT is a five-item, simple, patient-based tool for identifying subjects with poorly controlled asthma assessing asthma symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning. It has been validated and is available in several languages [15]. The ACQ is a seven-item questionnaire with the aim of assessing asthma control basing on asthma symptoms, awakening during the night due to asthma, activity limitations, use of bronchodilators and respiratory function values. It has been validated and is available in several languages [14].

The Control of Allergic Rhinitis and Asthma Test (CARAT) was developed for use in the concurrent management of these diseases, as recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [43]. A short 10-item version has been validated as a simple tool for measuring the degree of asthma and allergic rhinitis control in adult patients, by assessing symptoms frequency, sleep impairment, activities limitation and need for more medication [16]. CARAT has adequate properties to assess patients over time [44], and it has been validated and adapted for use in 15 countries. It is now in the process of validation for use in children and dissemination in primary care [45].

Specifically with regard to children, questionnaires about asthma have recently been used in epidemiological surveys, but only a few have been validated. The Paediatric Asthma Quality of Life Questionnaire for children (PAQLQ), derived from the AQLQ, has 23 items in three domains (symptoms, activity and emotional function). The PAQLQ is the only questionnaire for asthmatic children that addresses asthma-related QoL comprehensively; limited validation work has been published, even though its performance is considered adequate [46]. With regard to asthma control, three questionnaires need to be mentioned. 1) The Childhood Asthma Control Test (C-ACT), a seven-item questionnaire assessing asthma

control in children aged 4–11 years [47]. The C-ACT offers a promising tool, although it requires further validation as there is debate regarding the accurate estimation of poorly controlled asthma [46]. 2) The Asthma Control in Children questionnaire (CAN), a caregiver-/parent-completed questionnaire consisting of nine items on the child's general feeling within the past month for patients aged 2–14 years. It has been validated for use in clinical practice and research [48]. 3) Respiratory and Asthma Control in Kids (TRACK), a valid, easy, caregiver-completed questionnaire for preschool-aged children regarding the frequency of respiratory symptoms, activity limitation and night-time awakenings in the past 4 weeks, as well as the use of medication [49].

Lung function testing

Impaired respiratory function may be a consequence of diseases in the airways and/or lung parenchyma. Lung function tests measure different aspects of respiratory function but do not directly lead to an aetiological diagnosis in an individual subject [50]. In respiratory epidemiology, lung function tests are mainly used: 1) to detect lung function differences between groups or populations with different characteristics or living in different environments; 2) to assess longitudinal changes in lung function in the same subjects followed-up over time; 3) to validate subjective complaints collected by questionnaires in occupational or environmental settings; 4) to assess relationships between respiratory function and risk factors; or 5) to derive reference values for respiratory function. Analysing respiratory function data from epidemiological studies not only has pulmonary outcomes; for example, in population-based studies reduced lung function has been shown to be a marker for cardiovascular mortality, independent of age, sex and smoking history [51–53]. A review aiming to provide guidelines for improved measurements and a physiological background for interpretation of the results in respiratory epidemiology has published previously [54].

Standardisation

Variability of measurements is a critical feature of lung function testing. Sources of variability may be grouped as follows [55]: 1) technical variation related to an instrument, software, temperature, altitude, procedure, technician, subject and interaction between the technician and subject; and 2) biological variation including both intra-individual variations (*i.e.* body and head position, effort to perform the manoeuvre and circadian rhythm of lung function) and inter-individual variations (*i.e.* sex, age, race, anthropometric measurements, health status, socioeconomic status, exposure to environmental and occupational pollution).

To minimise technical variability of lung function testing measurements, standardised procedures have been developed. They encompass a number of steps, which include: equipment performance criteria; equipment validation; quality control; subject manoeuvres; measurement procedures; acceptability; repeatability; and reference value/interpretation [56].

The procedures of standardisation have continued to advance as a result of scientific studies that have provided additional data relating to performance of lung function testing. In 1960, the ECSC first published recommendations for performing lung function testing [57], while in 1978, within the Epidemiology Standardization Project of the DLD/NHLI, it was first published a document on standardised procedures to be used in epidemiological studies [58]. Several European and US documents on standardisation of lung function testing have subsequently been published [59–62]. Current guidelines were published jointly by the ATS and the European Respiratory Society (ERS) in 2005 [56, 63, 64]. In 2011, a Task Force of the

ERS Occupation and Epidemiology Assembly produced recommendations for the performance of general population studies on COPD, including lung function testing [34]. It was recommended to: 1) always carry out spirometry; 2) perform other lung function measurements depending on the specific aim of the study; 3) perform lung function measurements according to current ATS/ERS guidelines; and 4) obtain reference values from studies of normal subjects of the same sex, age, height and ethnic characteristics as those being studied.

Epidemiological studies offer the opportunity to evaluate the efficiency of standardised procedures for lung function testing. Within the Pollution Effects on Asthmatic Children in Europe (PEACE) study performed in 14 European centres, eight to 15 individuals performed FVC manoeuvres following a standard protocol with both the local instrument and a portable spirometer as a quality control procedure, disclosing a systematic overestimation of measurements due to technical problems in one instrument [65]. Within the international BOLD study (~10 000 subjects), a good quality of spirometry was reached, despite a diversity of settings, languages and ethnicity; ~90% of the subjects met the 2005 ATS/ERS goal of acceptability [66]. Within the PLATINO study, centralised quality control was shown to be performed *via* e-mail with good reliability and low cost [67]. A population-based study in Canada in >5000 subjects showed that good quality spirometry tests were attainable by trained research assistants, irrespective of their prior experience in spirometry, highlighting the importance of spirometry training with standardised coaching [68].

Reference values

Since lung function varies with age, height, sex and ethnicity, for interpretative purposes, test results need to be compared to reference values that are appropriate for the individual being tested [50]. Reference values are calculated using equations derived from measurements of lung function observed in representative samples of "normal" or "healthy" subjects selected from the general population.

Normal subjects are selected among participants in epidemiological surveys by applying selection criteria, which usually include: not reporting respiratory symptoms (*e.g.* cough, phlegm, dyspnoea and wheeze); history of physician diagnoses of respiratory diseases (*e.g.* COPD, asthma and TB); and hospitalisation due to pulmonary or thoracic diseases, smoking habit, and working exposure to dusts, gases or fumes [55]. Such information is collected using standardised questionnaires. The proportion of selected normal subjects decreases in older age, particularly among males aged >50 years [69], and an even smaller proportion of normal subjects may be selected in longitudinal studies [70].

There is a vast literature on studies of reference equations for lung function testing, conducted worldwide in populations of different ethnicity and age ranges. ATS and ERS documents, which summarise studies on reference equations for spirometry, lung volumes and diffusing capacity, have been published previously [50, 55]. In selecting appropriate reference values, the 2005 ATS/ERS guidelines recommend choosing the same source for all indices of interest, which used similar instruments and had a test population that included the age range, sex and ethnic group of individuals to be tested [71]. In the USA, the reference equations of the National Health and Nutrition Examination Survey (NHANES) III [69] and WANG *et al.* [72] are recommended for those aged 8–80 years and <8 years of age, respectively, while specific reference equations are not recommended in Europe, even though it is acknowledged that those most often used are the 1993 ERS summary equations [50].

The lack of a recommendation for the use of the 1993 ERS equations in Europe is due to the evidence that these equations can lead to overestimation of the results of respiratory function tests, especially in older ages [73, 74]. Demonstrated limits of the 1993 ERS equations include the following: 1) they were calculated from more than 20 series of equations published between 1950 and 1980 (cohort effect); 2) they were derived from existing equations and not from the original observed data of respiratory function; 3) the parameters inspiratory/expiratory slow vital capacity (VC), FVC and, as a result, FEV1/VC or FEV1/FVC ratios were all considered to be equivalent as in several original publications it was not clearly stated from which manoeuvre (*i.e.* slow or forced, inspiratory or expiratory) the single parameter derived; 4) they are suggested to be used in subjects aged 18–70 years and, by extrapolation, also in individuals aged >70 years, even though the equations were calculated for subjects aged 25–70 years.

In epidemiological studies, using reference equations that are not population-specific and instrument-specific may lead to biased estimates of the prevalence of COPD, as defined according to the ATS/ERS criterion, which is based on the use of the predicted values (*i.e.* airways obstruction having a ratio of FEV1 to slow VC lower than the 5th percentile of the normal distribution) [75].

With the aim to establish improved international spirometry reference equations, an ERS Task Force recently published the "Global lung function 2012 equations" for patients aged 3–95 years for some spirometric parameters (*i.e.* FEV1, FVC, FEV1/FVC, and mean forced expiratory flow between 25% and 75% of FVC), which include appropriate age-dependent lower limits of normality [76]. They were derived from 72 collated sets of original lung function data, collected in 26 countries from five continents, out of a total of 74 187 subjects divided into eight ethnic groups using the GAMLSS statistical model (www.lungfunction.org/files/GAMLSS-in-action.zip), which produces continuous equations over the entire age range tested [76].

Applicability in respiratory epidemiology

Spirometry, *D*LCO, PEF, single breath nitrogen test (SBN_2) and the methacholine challenge test have been used in population-based studies for obtaining data on lung function. The main advantages and disadvantages of these manoeuvres are reported in table 3. A Medline search conducted in April 2014 revealed that, in the past 14 years, the most common lung function tests performed in epidemiological studies were those based on the forced expiration (19%) and slow manoeuvre (12%) (table 4).

Spirometry

Among the various lung function parameters, FEV1 has been demonstrated to be the parameter of choice. It is simple and acceptable for the subjects, requires only a few minutes to perform and has a strong reproducibility, allowing serial measurements for the follow-up of physiological decline of ventilatory function to be performed, as well as monitoring of the progression of obstructive pulmonary diseases and response to treatments [36, 54, 56]. Moreover, FEV1 has a prognostic value in respiratory diseases, such as COPD [77], and for all-cause [78] or cardiovascular mortality [51]. Thus, spirometry has been included in many large population-based studies conducted worldwide in general population samples for wide age ranges, from childhood to the elderly [24, 66, 79–82].

Table 3. Advantages and disadvantages of lung function testing in epidemiological studies

Test	Advantages	Disadvantages
Spirometry	Simple and acceptable for subjects of all ages Inexpensive Easily and rapidly performed Strong reproducibility Gold standard for diagnosing airways obstruction Prognostic value Useful for longitudinal measurements	Limits in comparison analyses between studies using different type of instruments or protocols of measure
***D*LCO**	Noninvasive test of pulmonary gas exchange Sensitivity indicator Useful for longitudinal measurements	Within-individual and between-laboratory variability Difficult to perform in large samples
SBN_2	Assessment of small airways	Difficult to obtain acceptable manoeuvres Little or no advantages with respect to spirometry
PEF	Self-administration Well accepted Inexpensive Prognostic value Possibility of repeated measurements over time (within a day and over several days)	Not able to asses bronchodilator response Not interchangeable with FEV1
Methacholine challenge test	Well standardised Predictive value for developing asthma	Need of trained staff and appropriate laboratory

SBN_2: single-breath nitrogen test.

Spirometry has been demonstrated to be applicable in populations of elderly subjects. In an Italian sample of 1612 subjects aged $\geqslant$65 years, ~80% of tests with at least three acceptable curves were obtained, while percentages of reproducible tests ranged from 87.6% to 95.8% for FEV1 by applying a rigorous quality control programme [83]. Most schoolchildren aged $\geqslant$9 years participating in the Children's Health Study (a 10-year longitudinal investigation of >5000 subjects) performed forced expiratory spirometric manoeuvres well enough to meet established adult-based manoeuvre criteria for within-test session manoeuvre reproducibility [84]. Reproducible flow–volume curves in young children aged 2–6 years have also been obtained [85].

D*LCO*

There are few epidemiological studies in which *D*LCO has been measured. In a Norwegian community study, it was shown that 67% of participants fulfilled the ATS criteria for a successful *D*LCO measurement [86]. In the same epidemiological study, relationships between risk factors such as socioeconomic status or inflammatory markers and *D*LCO have been assessed [87, 88]. *D*LCO was demonstrated to discriminate symptomatic from asymptomatic subjects and smokers from nonsmokers in the Po river delta study in Italy [89]. Also longitudinal measurements of *D*LCO have been obtained. In both the Tucson (Arizona, USA) [90] and the Po river delta study [91], analyses of *D*LCO data obtained 8 years apart consistently showed that *D*LCO decline accelerates with age, regardless of sex, smoking status and the initial level of lung function. In the large sample of subjects (n=4333) participating in

Table 4. Use of lung function testing in respiratory epidemiology from 2000 to 2014, according to a Medline search conducted in April 2014

Search no.	Search terms	Retrieved references
1	''Epidemiology'' AND ''Respiratory'' AND (''Lung function'' OR ''Pulmonary function'')	8938 (100)
2	AND (''Spirometry'')	960 (11)
3	AND (''Forced expiratory volume'' OR ''FEV_1'')	1690 (19)
4	AND (''Forced vital capacity'' OR ''FVC'')	1293 (14)
5	AND (''Vital capacity'' OR ''VC'')	1055 (12)
6	AND (''Transfer factor'' OR ''Diffusing capacity'' OR ''D_{LCO}'')	277 (3)
7	AND (''SBN_2'' OR ''Single breath nitrogen test'')#	0 (0)
8	AND (''Peak expiratory flow'' OR ''PEF'' OR ''PEFR'')	284 (3)
9	AND (''Peak flow variability'')	26 (<1)
10	AND (''Methacholine challenge test'' OR ''BHR'')	115 (1)

Data are presented as n (%). Search no. 2–10 includes the terms from search no. 1 and the additional terms. VC: vital capacity; SBN_2: single breath nitrogen test; PEFR: peak expiratory flow rate. #: no papers published after 1998 were found in a Medline search.

NHANES, aged 25–74 years at the time of baseline survey and with a mean follow-up of 12.8 years, it has been observed that a reduction of 5 $mL \cdot min^{-1} \cdot mmHg^{-1}$ D_{LCO} was associated with a 17% significant increase in mortality after adjustment by sex, race, age, cholesterol, systolic blood pressure, current smoking, moderate alcohol consumption and BMI [92]. More recently, D_{LCO} was shown to be a sensitive indicator of the long-term effects of intermediate levels of α_1-antitrypsin on lung function, especially in elderly smokers, as compared to FEV_1. Smokers with the heterozygous deficient allele (PiMZ) of α_1-antitrypsin were at greater risk of lung function abnormality, as assessed by D_{LCO}, from middle to late adult life [93].

Single breath nitrogen test

In the 1970s, SBN_2 was used to attempt early detection of the "small airways diseases" due to cigarette smoking. Reference values for SBN_2 were also derived [94–96]. Controversial results were found in cross-sectional studies [96, 97]. Few longitudinal studies have evaluated the relationship between baseline measurements from the SBN_2 test and rates of lung function decline [98, 99]. In a general population sample, an increase in the slope of phase III of the SBN_2 test in moderate smokers was shown to be predictive of a 50% increase in the rate of decline in FEV_1 [98]. After the 1980s, the prevalent opinion was that the SBN_2 test offered little or no advantage over monitoring *via* spirometry. Moreover, the use of the SBN_2 test was found to be unsuitable in epidemiology, due to the difficulty in obtaining acceptable measurements, especially in children [94, 100].

PEF

PEF monitoring has frequently been used to assess the effects of different factors (including air pollutants) on airway calibre. PEF is easy to perform, inexpensive and well tolerated. It also allows for the collection of a large number of measurements within a day and over several days, in relation to different potential trigger factors. PEF and FEV_1 are not

interchangeable; PEF is not able to assess bronchodilator response compared to FEV_1 [6]. The linearity and the accuracy of different PEF meters have been extensively evaluated, in general showing a high reproducibility and repeatability of the measurements [6]. PEF can have a prognostic value. A longitudinal repeated-measurement study in school-aged children showed that a reduction in PEF values and frequency of respiratory symptoms were higher in the school closer to major stationary air pollution sources than in the distant school [101]. More recently, a 15-year follow-up of 17 000 Chinese subjects showed that a decrease in the height-adjusted PEF value was associated with higher risk of mortality from respiratory and other causes, including lung cancer and cardiovascular disease [102].

Methacholine challenge test

Measurement of nonspecific BHR has successfully been used in field studies over wide age ranges from childhood to elderly age (*e.g.* 8–74 years) [103]. Several methods exist, but methacholine and histamine are the agents of choice because they are widely used and the methods are well standardised. BHR appears to be related to the development of COPD and it is also an important characteristic of asthma. Exposure to host factors (sex and age) [104] and environmental factors (smoking habits, occupational exposure, infections and air pollution) can influence BHR [103]. Segregation analyses have suggested a gene–environment interaction between BHR and smoking [105]. Epidemiological studies have concluded that BHR is also associated with an enhanced risk for accelerated decline in FEV_1 [106] and can be a significant predictor of active asthma in children, as observed after 6 years of follow-up [107].

Conclusion

Questionnaires and lung function testing are the most important instruments for obtaining subjective and objective data in respiratory epidemiological surveys. These tools have demonstrated their usefulness for many decades, providing basic respiratory data to be analysed for several research objectives.

Many modified versions of standard questionnaires or specially designed questionnaires have been developed. An effort to produce a standardised questionnaire for use in all new epidemiological respiratory surveys should be performed, in order to facilitate comparison analyses between different studies.

Lung function tests in epidemiology should not be limited to spirometry; a comprehensive study of respiratory function may reveal a better understanding of lung physiology for epidemiological outcomes.

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Inflammation and allergy related to bronchial hyperresponsiveness

Christer Janson[1] and Andrei Malinovschi[2]

BHR is one of the hallmarks of asthma. In asthmatic patients, BHR is often regarded as a consequence of airway inflammation, but BHR is also found in other disorders such as COPD, where the association with airway inflammation is less clear. The aim of this chapter is to investigate how allergy and inflammation, together with nonallergic exposures such as smoking, are related to BHR.

The median prevalence of BHR was 13% in the European Community Respiratory Health Survey, but the study also showed an eight-fold variation in BHR between the centres. Urban living, female sex, higher age and obesity have been associated with a higher prevalence of BHR. Allergic sensitisation to perennial allergens, such as cats and mites, and smoking increase the likeliness of having BHR. BHR is related to increased levels of eosinophilic inflammatory markers in blood and sputum and to increased *F*eNO. The association between *F*eNO and BHR is, however, only found in nonsmokers and in subjects who are atopic. BHR is related to neutrophil inflammation in COPD.

We conclude that allergy and smoking are the main determinants of BHR, but the type of inflammation in BHR associated with smoking is different from the type of inflammation in BHR associated with allergy. BHR that is associated with allergy is related to eosinophilic inflammation and high *F*eNO, while neutrophilic inflammation is important in smoking-associated BHR.

BHR (also known as bronchial hyperreactivity or airway hyperresponsiveness) is one of the hallmarks of asthma. BHR is usually present in both allergic and nonallergic asthma [1]. In asthma, BHR is often regarded as a consequence of airway inflammation, but BHR is also found in other disorders, both respiratory [2] and nonrespiratory [1], where the association with airway inflammation is less clear. Apart from allergy, smoking is also an important determinant of BHR [3]. The aim of this chapter is to investigate how allergy and inflammation, together with nonallergic exposures such as smoking, are related to BHR (fig. 1).

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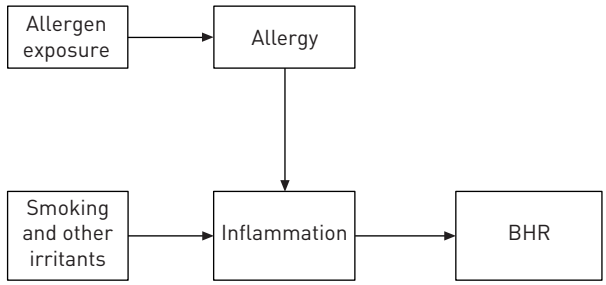

Figure 1. Association between inflammation and BHR in relation to allergy and smoking.

BHR and bronchial responsiveness

Definition

BHR is defined as airway narrowing in response to a stimulus that would be innocuous in a normal person [4]. The relative fall in FEV_1 to a predefined threshold concentration or accumulated dose of the provocative stimulus is used when assessing BHR. When the provocative agent is methacholine, the accumulated dose needed to give a 20% fall in FEV_1 (PD_{20}) is often used. An alternative method is to estimate the concentration of methacholine needed to give a 20% fall in FEV_1 (PC_{20}) [5]. The relative decrease in FEV_1 used when defining BHR differs between different methods and agents; as an example, a 15% decrease is usually used when defining BHR using mannitol challenge [6].

The concept of BHR has, however, substantial limitations, since the majority of subjects do not reach the critical threshold level so that their degree of responsiveness cannot be expressed in terms of a critical dose. An alternative way of expressing a patient's reaction to a provocation test is to measure bronchial responsiveness (BR). Different methods for measuring BR are used, but they often take into account both change in FEV_1 and the accumulated dose [7, 8], as response–dose ratio or dose–response slope. These methods are useful in population-based studies where only a small proportion of subjects achieve a 20% fall in FEV_1 and allow both asthmatic and normal people to be taken into account when assessing risk factors for BR.

BHR is a characteristic feature of asthma [4], but BHR is also associated with other diseases, such as COPD [2, 9], rhinitis [10], cardiovascular disease [11] and rheumatological diseases such as Sjögren's disease [12]. Having BHR is also related to increased risk of developing respiratory diseases such as asthma, COPD and rhinitis [13–15], as well as having a negative effect on lung function growth and decline [16–18].

Indirect and direct challenge methods

Bronchial challenge agents can be divided into direct and indirect stimuli on the basis of their mechanism of action. Direct stimuli, such as methacholine and histamine, cause airway narrowing by acting directly on specific receptors on the bronchial smooth muscle. Indirect stimuli, such as cold air, mannitol and AMP, cause airflow limitations as a result of mediator release from inflammatory cells, which results in both airway wall thickening and smooth muscle contraction. In one study from Sweden, patients with allergic and nonallergic asthma had the same response to direct stimuli (methacholine), while the response to indirect stimuli

(AMP and cold) was much more increased in the allergic asthmatics than in the nonallergic asthmatics [1]. Other comparisons of direct and indirect challenge have found that direct tests are more sensitive, while indirect tests are more specific in relation to asthma [19]. When not otherwise mentioned, this chapter will mainly deal with the results of direct tests of BHR.

Epidemiology

Prevalence and geographical variation

The median prevalence of BHR ($PD_{20} \leqslant 1$ mg for methacholine) was 13% in the European Community Respiratory Health Survey (ECRHS), but the study also showed an eight-fold variation in BHR, with the highest prevalence in Hawke's Bay, New Zealand (27.8%) and the lowest in Galdakao, Spain (3.4%) (fig. 2). The geographical distribution of BR and BHR fitted well with that for asthma symptoms and disease [20]. In the ECRHS in Belgium, the prevalence of BHR was higher in Antwerp City than in suburban parts of southern Antwerp [21]. A higher prevalence of BHR in subjects living in urban than nonurban areas was also found in a study from Italy [22], whereas in the Netherlands the prevalence of BHR was higher in a rural than an urban area [23].

Studies comparing difference in BHR between eastern and western Europe have yielded conflicting results. The prevalence of BHR was higher in Tartu, Estonia than in Uppsala, Sweden [24], whereas NOWAK *et al.* [25] found that the prevalence of BHR was lower in Erfurt in former East Germany than in Hamburg. In a subsequent follow-up of the German study, the prevalence of BHR was found to have increased in subjects living in Erfurt, while BHR remained unchanged in the group of subjects from Hamburg [26]. This change may be attributed to changes in life style following the end of the cold war and the unification of Germany.

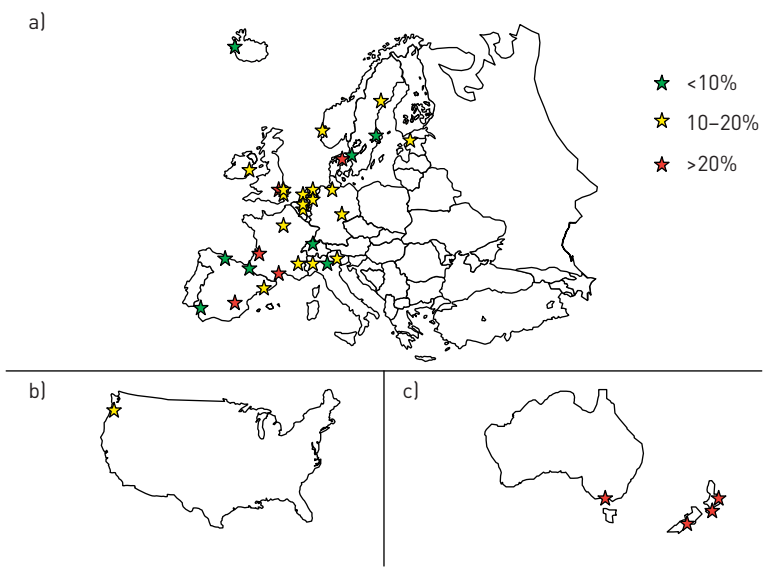

Figure 2. The prevalence of BHR (provocative dose causing a 20% fall in FEV_1 of $\leqslant 1$ mg for methacholine) in the European Community Respiratory Health Survey, in a) Europe, b) the USA and c) Australia and New Zealand. Data from [20].

Sex

In several studies, females had a higher prevalence of BHR [3, 25, 27, 28] and higher BR than males [22, 28]. In one study, this sex difference was explained by difference in airway geometry between females and males [29], while in other studies the prevalence of BHR remained higher in females even after adjustment of airway calibre [27, 28]. The reason for this sex difference is not clear. In animal models, oestrogen is related to decreased BR [30] while progesterone is related to increased BR [31]. An increase of BR has been suggested after menopause, and hormonal replacement therapy appears to reduce BR [32]. Effects of menstrual cycle and oral contraceptives in healthy females have been studied to a limited extent, but no effects on bronchial reactivity have been found [33].

Age

Several studies have found a higher increase of BHR in older than younger subjects [23]. BR also increased over a 10-year period in a longitudinal analysis of the ECRHS [34]. This might be related to a loss of the bronchoprotective effect of deep inspiration in the elderly [35]. Other studies indicate that the age relationship may be U-shaped, with higher BR to methacholine in the youngest and oldest age groups [22].

BMI

KWON *et al.* [36] reported that increased BMI was related to a higher level of BR in a large cohort of asthmatics. No differences in BR to either direct or indirect stimuli were found between obese and non-obese subjects with asthma in a pooled analysis of severe asthma cohorts [37]. A recent cluster analysis study suggests that obese asthmatic adults differ in terms of BHR, as only obese subjects with uncontrolled asthma had lower BR than non-obese asthmatics [38]. Furthermore, even the age of asthma onset appears to modulate this relationship, as obese subjects with early onset asthma had BHR to a larger extent than subjects with late onset of asthma [39]. There is also no consensus on the effects of BMI on BR in healthy adults, as contradictory results have been reported [40–42]. A previous study performed using the ECRHS material reported that there might be sex differences, as an effect of BMI on BR was predominantly seen in males but not females [42]. A recent study suggests that BMI is related to BHR in patients with allergic rhinitis, since a BMI >25 kg·m^{-2} was related to an odds ratio for having BHR that was 3.3 times higher in this patient category [43].

Smoking

Smoking has been found to be an independent determinant of BHR in cross-sectional epidemiological studies [3, 25, 44, 45]. A dose-dependent association between amount of smoking and BHR was found in a Finnish population study [46]. LEYNAERT *et al.* [27] reported that females who were heavy smokers had an increased risk of moderate-to-mild BHR, but that no such association was found in males. In an analysis of longitudinal data, CHINN *et al.* [34] found an increase in BR in persistent smokers. Improvement in BHR after smoking cessation has been found in asthmatics [47] and COPD patients [48] and passive smoking has been associated with BHR both in children [49] and adults [50]. There are also data supporting a gene–environment interaction between BHR and smoking [51].

Smoking is also related to higher prevalence of BHR when assessed by indirect agents such as mannitol. For example, reactivity to mannitol was found in 26% of healthy smoking adults compared to 2% of nonsmoking subjects [52]. Smoking cessation leads to decreased reactivity to mannitol in healthy subjects [52] and a decreased responsiveness to AMP in COPD patients [48]. The prevalence of mannitol reactivity is also high in smoking asthmatics, as it has been reported to be 70% in a recent study of steroid-naïve, smoking asthmatics [53].

The mechanism for this relationship between smoking and BR to mannitol is not clear, but it might involve activation of mast cells, as suggested in one study [54].

Environmental exposure

Occupational exposure to isocyanates is related to BHR [55] and a high prevalence of BHR has been found in occupations such as painters [56] and firefighters [57]. For example, short-term exposure to materials generated during the collapse of the World Trade Center was associated with BR in firefighters and, furthermore, the degree of BR was related to the intensity of the exposure [58]. Occupational endotoxin exposure has also been related to BHR [59]. Similarly, acute exposure to organic dust, such as swine dust, is related to the increase of BR in healthy adult subjects [60]. Nonetheless, BHR has been shown to be less sensitive than asthma-like symptoms in detecting a negative effect of the occupational exposure [61].

Household exposure may also play a role and BHR has been related to living in a dwelling with newly painted wood details or kitchen painting [62], exposure to terpenes [63] and viable moulds [64]. In COPD, exposure to wood smoke is associated with more severe BHR than in COPD patients exposed to tobacco [65]. An association between outdoor air pollution and BHR has also been found in several studies [66, 67].

BHR and allergy

A higher prevalence of BHR in atopic than nonatopic subjects has been found in many studies [44, 68, 69]. The attributable risk of atopic sensitisation for BHR was found to be 19% in Sweden and 21% in Spain [68, 69]. Cat sensitisation was the allergen most strongly associated with BHR in Sweden and in the Netherlands [68, 70, 71], while in India, Belgium and the UK the association with BHR was strongest for mites [21, 28, 72]. In the ECRHS, mite sensitisation was the most important for BHR in 15 centres, cat in eight, cat and mite equally in one, timothy grass in eight and *Cladosporium* in two centres. Total IgE has been associated with BHR independently of specific IgE in several studies [73–75]. Exposure to cat allergens was found to be related to increase of BR in atopic subjects studied 10 years apart [76] and improvement in BHR after cat immunotherapy has been reported [77].

BHR and inflammation

Pathophysiology

In asthma, BHR is thought to be related to airway inflammation and airway remodelling [78]. A schematic model of this relationship has been presented in a previous review [79] and is shown in a modified version in figure 3. Less is known of the pathophysological mechanism in nonasthmatic BHR.

Inflammatory markers

The association between inflammatory markers and BHR has been investigated in a large number of studies (table 1).

Blood, serum and plasma

The number of eosinophils in blood has been found to correlate significantly with BHR measured with methacholine [80, 81], histamine [82–84] and hypertonic saline [85] in

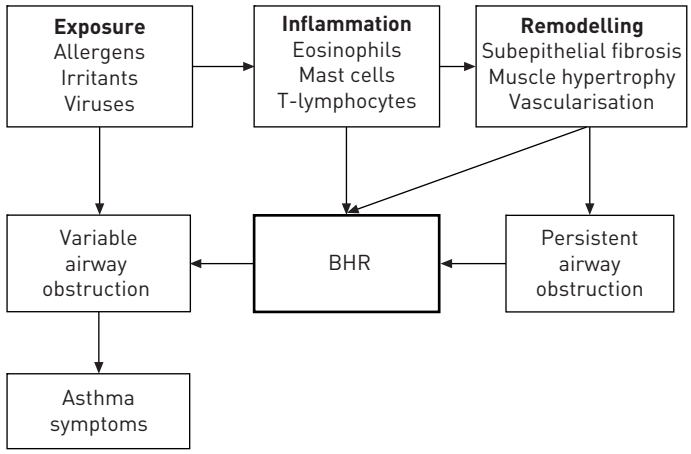

Figure 3. Mechanism of how inflammation and remodelling affect BHR. Reproduced and modified from [79] with permission from the publisher.

studies of patients with asthma. An association between blood eosinophil number and BHR has also been found in many epidemiological studies [23, 86–88]. A correlation between the level of BHR and eosinophil cationic protein (ECP) has been found in some investigations [89–91], while other studies have reported a negative result [80, 85]. Studies comparing the sensitivity of different eosinophil markers have yielded conflicting results. Some studies have indicated that serum ECP or serum eosinophil peroxidase may be more strongly correlated with BHR than blood eosinophil number [92–94], while other investigations have indicated the opposite [80, 85].

Table 1. Inflammatory markers associated with BHR

Compartment	Marker	Level of association	Comments
Blood	Eosinophil number	+++	
	ECP	++	
	EPO	+	
	MPO	+	
	Basophil number	+	
	Monocyte number	+	
	CRP	+	
	IFN-γ	+	
Sputum	Eosinophil number	+++	
	ECP	++	
	Metachromatic cell number	+	
	Neutrophil number	+	Only in COPD
Exhaled air	Nitric oxide	++	Only in nonsmokers and in atopic subjects
	Hydrogen peroxidase	+	

ECP: eosinophil cationic protein; EPO: eosinophil peroxidase; MPO: myeloperoxidase; CRP: C-reactive protein; IFN: interferon; +++: consistent in several studies; ++: consistent in most studies; +: inconsistent or only one study.

A correlation between serum levels of myeloperoxidase and BHR has been found in one study [95]. Higher C-reactive protein levels have been found in subjects with BHR in France [96] but not in a study using a similar protocol with participants from Sweden, Estonia and Iceland [97]. Plasma levels of interferon-γ correlated significantly with BHR in one study [98]. In another study comprising allergic asthmatics, the fall in FEV_1 after hypertonic saline provocation correlated both with the number of basophils and with the number of monocytes [85]. The number of basophils also correlated with PC_{20} methacholine [85].

Sputum and saliva

Levels of sputum eosinophils and sputum ECP have been found to correlate significantly with the level of BHR [45, 99–104]. Comparison between methacholine and mannitol provocations shows a closer correlation between eosinophil inflammation and mannitol than between eosinophils and methacholine [105]. A significant correlation between PC_{20} and the number of metachromatic cells (mast cells and basophils) in sputum was found in one study [99]. An association between levels of sputum neutrophils and BHR has been found in patients with COPD [9], whereas no such association was found in a study of stable asthmatics [103]. Salivary ECP was found not to be associated with asthma severity and did not correlate with serum ECP [106].

Exhaled air

F_{ENO} values have been found to correlate significantly with BHR (methacholine) in patients with asthma [102, 107] and in patients with respiratory symptoms [108]. Correlations between F_{ENO} and BHR measured by methacholine [109], histamine [46] and mannitol [110] have been shown in studies of populations of nonsmokers. F_{ENO} and bronchial reactivity to mannitol are related to a stronger degree than F_{ENO} and bronchial reactivity to methacholine [105]. In a Danish population-based study, all young adults with F_{ENO} <20 ppb were unreactive to mannitol [110]. However, in patients with respiratory symptoms that were investigated for asthma, significant numbers (26%) of those with a low F_{ENO} were reactive to mannitol [111].

Measuring H_2O_2 in exhaled breath condensate has been proposed as a noninvasive marker of oxidative stress in the airways. Levels of H_2O_2 were found to correlate significantly with the level of BHR in one investigation [112].

BHR inflammation: interactions with allergy and smoking

In allergic subjects, BHR is associated with eosinophilic inflammation. The association between allergy and BHR, however, probably also involves other inflammatory mediators than eosinophils, since IgE sensitisation and eosinophil inflammation have been found to be associated with BHR independently of each other [113]. Higher levels of F_{ENO} are related to BHR, but in several studies this association has been found to exist only in atopic subjects [109, 114]. Other studies have found that higher F_{ENO} is only associated with BHR in nonsmokers [46, 109] and in fact, in one of these studies, F_{ENO} was actually negatively associated with BR in smokers [109]. Another indication of a possible interaction between smoking and allergy is the finding of SUNYER *et al.* [115], who found that smoking was associated with BR only in nonatopic subjects. This also fits in with data showing that smoking is a risk factor for nonallergic but not for allergic asthma [70]. BHR is related to neutrophilic inflammation in COPD [9] and neutrophilic inflammation has also been found to be a characteristic of nonallergic asthma [116]. It is therefore likely that neutrophils play an important role in the development of BHR in smokers.

Conclusion

We conclude that allergy and smoking are the main determinants of BHR, but the type of inflammation in BHR associated with smokers is different from the type of inflammation in BHR associated with allergy. BHR that is associated with allergy is related to eosinophilic inflammation and high $F_{E}NO$, while neutrophilic inflammation is important in smoking-associated BHR.

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